Implementation of

ISO/IDMP 11238 Substance Standard and Movement towards a Global Ingredient Archival System

GInAS

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Vision of 11238 Implementation

- **A single global registration system to identify Substances in Medicinal Products**
  - **A single global ID for substances and specified substances that is free to obtain and use;**
  - **New substances to be registered prior to submissions and referred to by the ID in a submission;**
  - **A single place for registration of substances and deposition of information related to substances (identification, analytical and manufacturing information and relevant biological data);**
  - **Data system managed by regulators from throughout the world;**
  - **Development of a freely distributable tool or data system to facilitate registration;**
  - **Common Messaging to communicate relevant substance information.**

Current Substance Registration System (EU/NL)

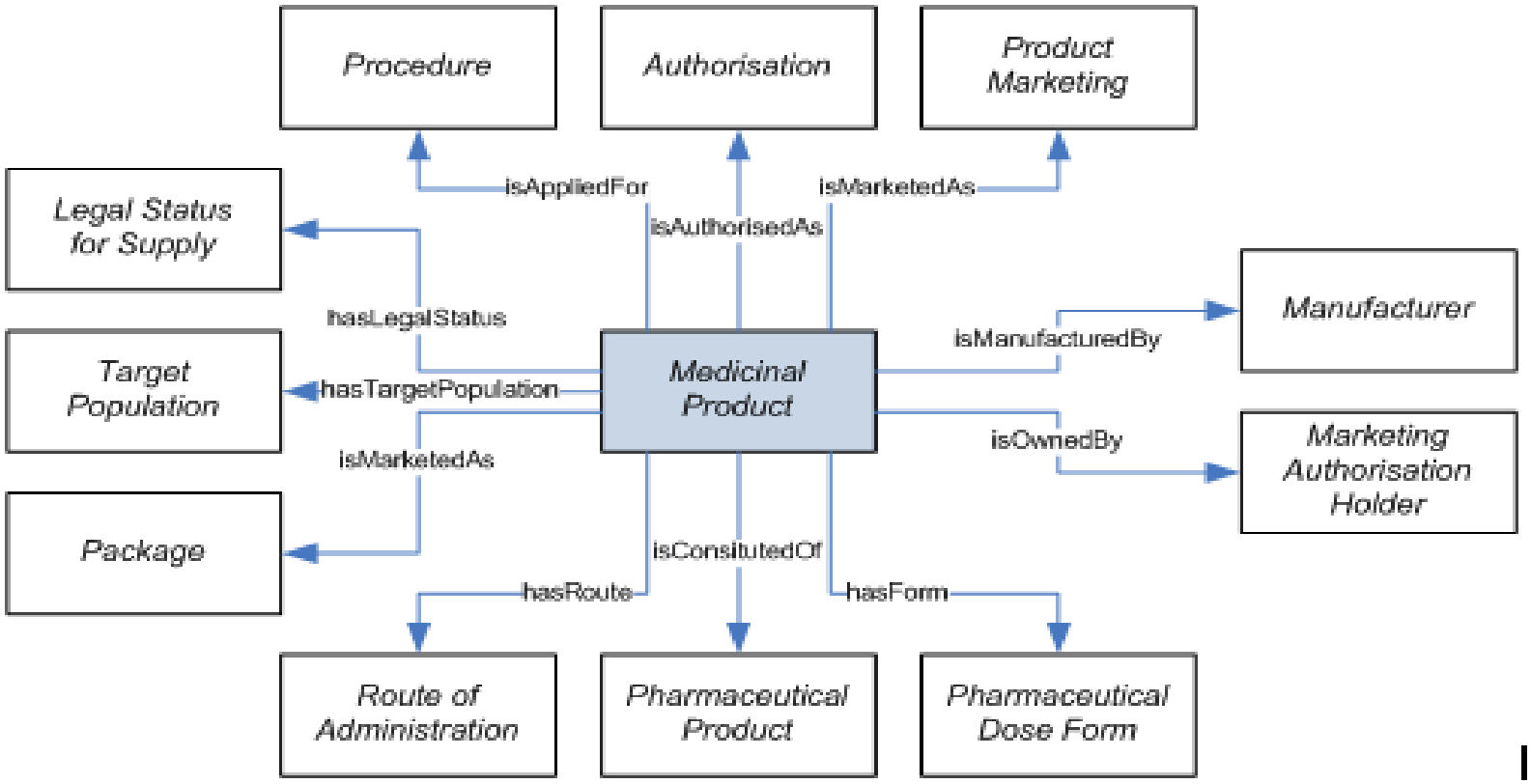


Figure 2-1: Relationships with Medicinal Product Business Concept

Current Substance Registration System (EU/NL)

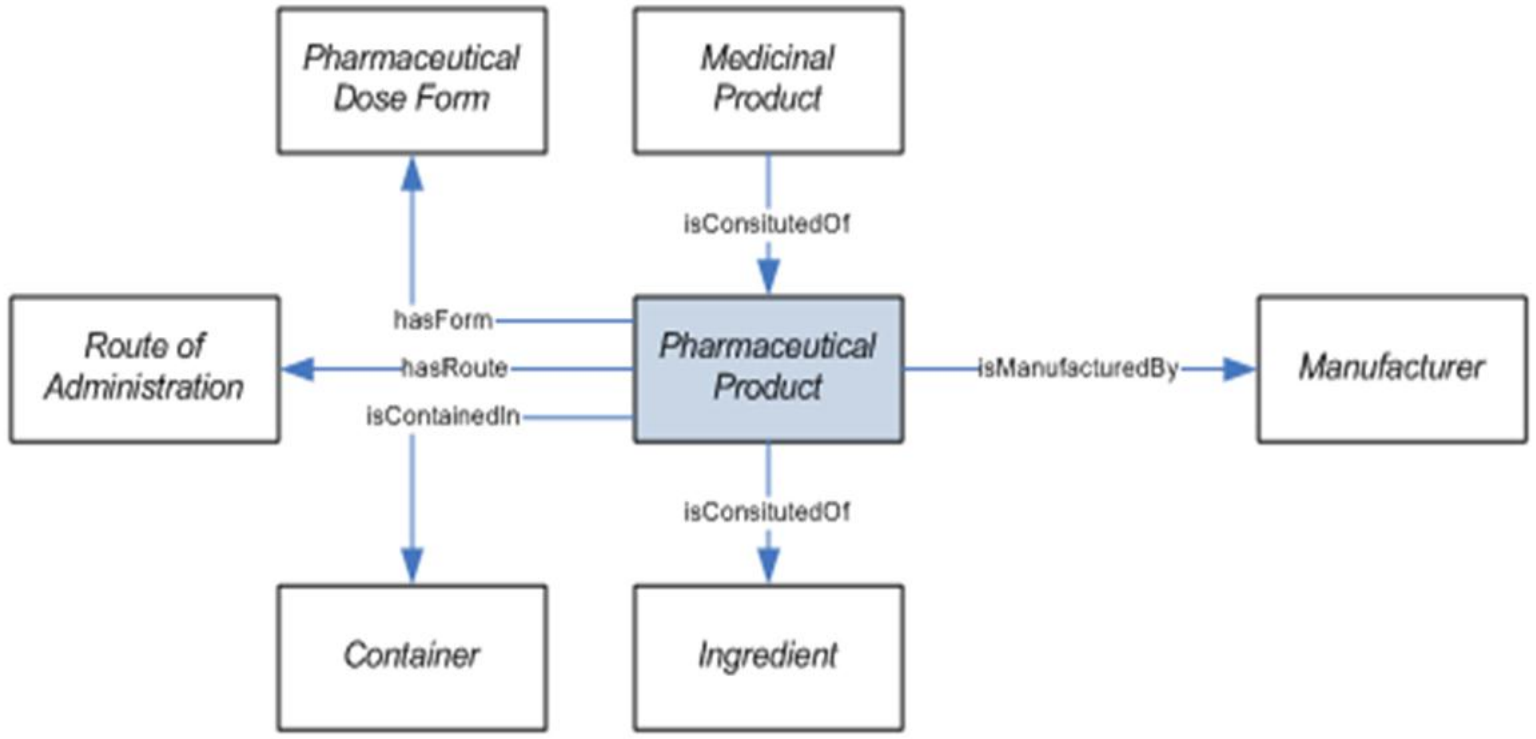


Figure 2-3: Relationships with Pharmaceutical Product Business Concept

Current Substance Registration System (EU/NL)

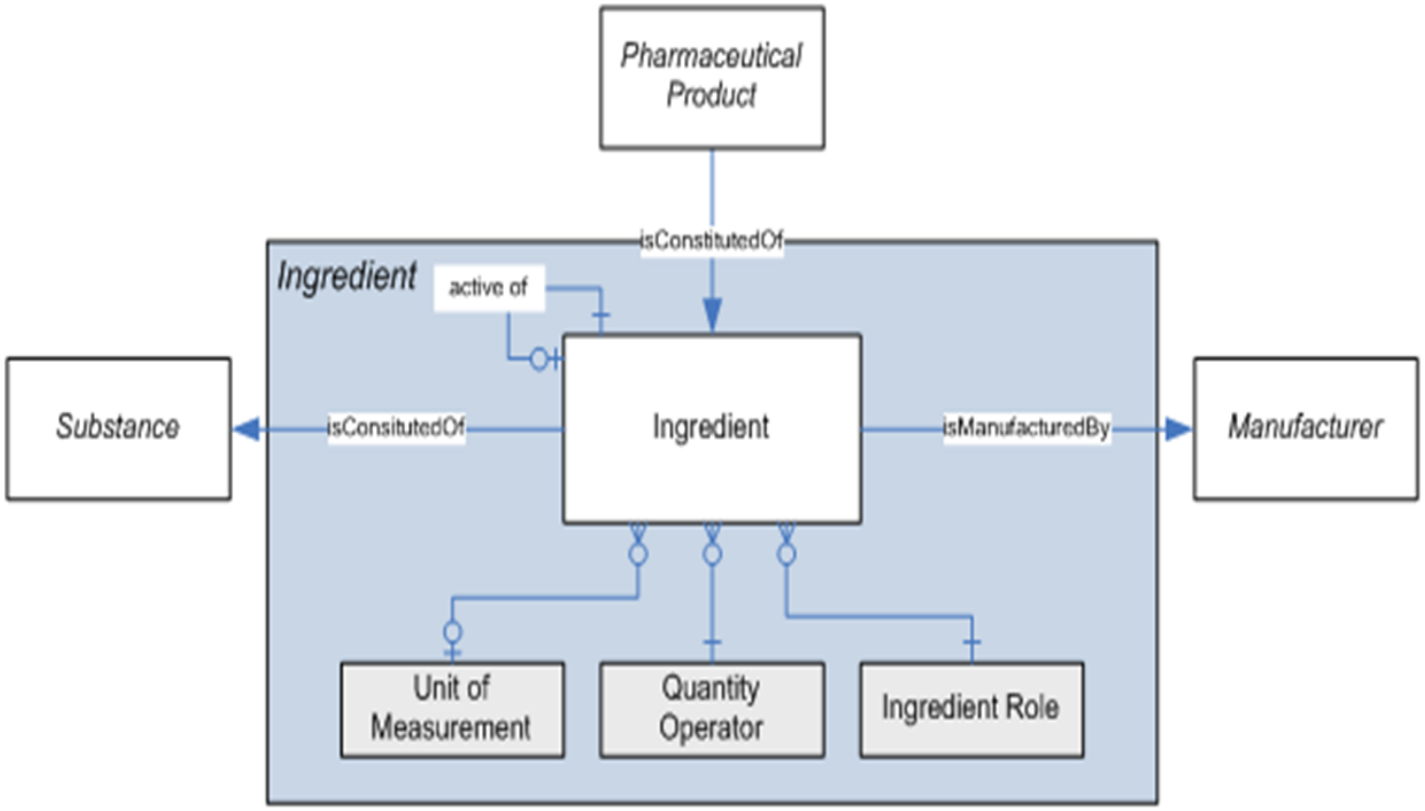


Figure 2-7: Link from Ingredient to Technical Concepts

(Active) Chemical Substance Record in “ICI”

Custom Object: 9999910182 - PERINDOPRIL-TERT-BUTYLAMINE

Close

Class: *Substance (readonly)*

Property	Value
CBG Number:	9999910182
CAS Number:	0107133368
Dutch Name:	PERINDOPRIL-TERT-BUTYLAMINE
Homeopatic Name:	
Preferred Term As Inactive Ingredient:	
Quantity Indicator Inactive Ingredient:	
P RMS:	
Harmonised Substance Data Lock Point:	
Active Ingredient Synonym:	"BUTYL(TERT)AMINOPERINDOPRIL"; "PERINDOPRIL TERT-BUTYLAMINE SALT"; "PERINDOPRILBUTYLAMINE (TERT)"; "S 9490-3"; "TERT-BUTYLAMINOPERINDOPRIL"; "1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro(2S,3aS,7aS)-comp.with 2-methyl-2propanamine (1:1)"; "Coversyl"; "2-Methylpropan-2-amine (2S,3aS,7aS)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate."; "Perindopril erbumine"
Origin:	
Latin Name:	PERINDOPRILUM TERT-BUTYLAMINUM
INN Name:	PERINDOPRIL-tert-BUTYLAMINE
English Name:	PERINDOPRIL-tert-BUTYLAMINE
Inactive Ingredient Name:	
Notes:	Mol. Gew.: 441,60 Mol. Form.: C19 H32 N2 O5 . C4 H11 N Polymorphism: De stof kan bestaan in een amorfe vorm (Manufactorer LEK) of in diverse crystallijne vormen; Alpha criystallijne vorm: Krka

Pharmaceutical Product Representation in “ICI” in Tablet

Filter folder for documents where: Show Advanced Criteria

Document Title contains

Apply Filter Clear

Actions Menu Items Found: 7 View: Detailed Show Items: 500

Title ▲	Quantity Value 1	Quantity Operator	Quantity Value 2	Unit	Ingredient Type	Composition Group
CELLULOSE, MICROKRISTALLIJN					Inactief bestanddeel	Samenstelling
INDAPAMIDE, 0-WATER 0,625 = mg/stuk	0,625	=		mg/stuk	Actief bestanddeel	Samenstelling
LACTOSE 1-WATER					Inactief bestanddeel	Samenstelling
MAGNESIUM STEARATE (E 470B) (RI)					Inactief bestanddeel	Samenstelling
NATRIUMWATERSTOFCARBONAAT					Inactief bestanddeel	Samenstelling
PERINDOPRIL-TERT-BUTYLAMINE 2 = mg/stuk	2,0	=		mg/stuk	Actief bestanddeel	Samenstelling
SILICIUMDIOXIDE (E 551)					Inactief bestanddeel	Samenstelling

Active Chemical Substance Representation in Pharm. Product

Class: Ingredient

	Property	Value
	Ingredient Type:	Actief bestanddeel
*	Substance:	9999910182 - PERINDOPRIL-TERT-BUTYLAMINE Change Value
	Quantity Value 1:	2,0
	Quantity Operator:	=
	Quantity Value 2:	
	Unit:	mg/stuk Change Value Clear
*	Concerned Pharmaceutical Product:	Co-Tomil 2 mg/0,625 mg, tabletten - 103269 - Tablet Change Value
	Equivalent Substance:	- PERINDOPRIL Change Value
	Equivalent Quantity Value 1:	1,668
	Equivalent Quantity Operator:	=
	Equivalent Quantity Value 2:	
	Equivalent Unit:	mg/stuk Change Value Clear
*	Composition Group:	Samenstelling
	Notes:	

Connection between Naming Active Substance "Dutch name field" and wording in Section 2 of SmPC

1. NAME OF THE MEDICINAL PRODUCT

<<Product name>> 2 mg/0.625 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg perindopril tert-butylamine equivalent to 1.67 mg perindopril and 0.625 mg indapamide.

Excipient:
Each tablet contains 33.74 mg lactose.
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Oblong, white, slightly biconvex tablets with bevelled edges.

ISO IDMP Standards (5)

- ISO 11238 Health Informatics — Identification of medicinal products — Data elements and structures Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances and specified substances

Scope

Together, these five standards:

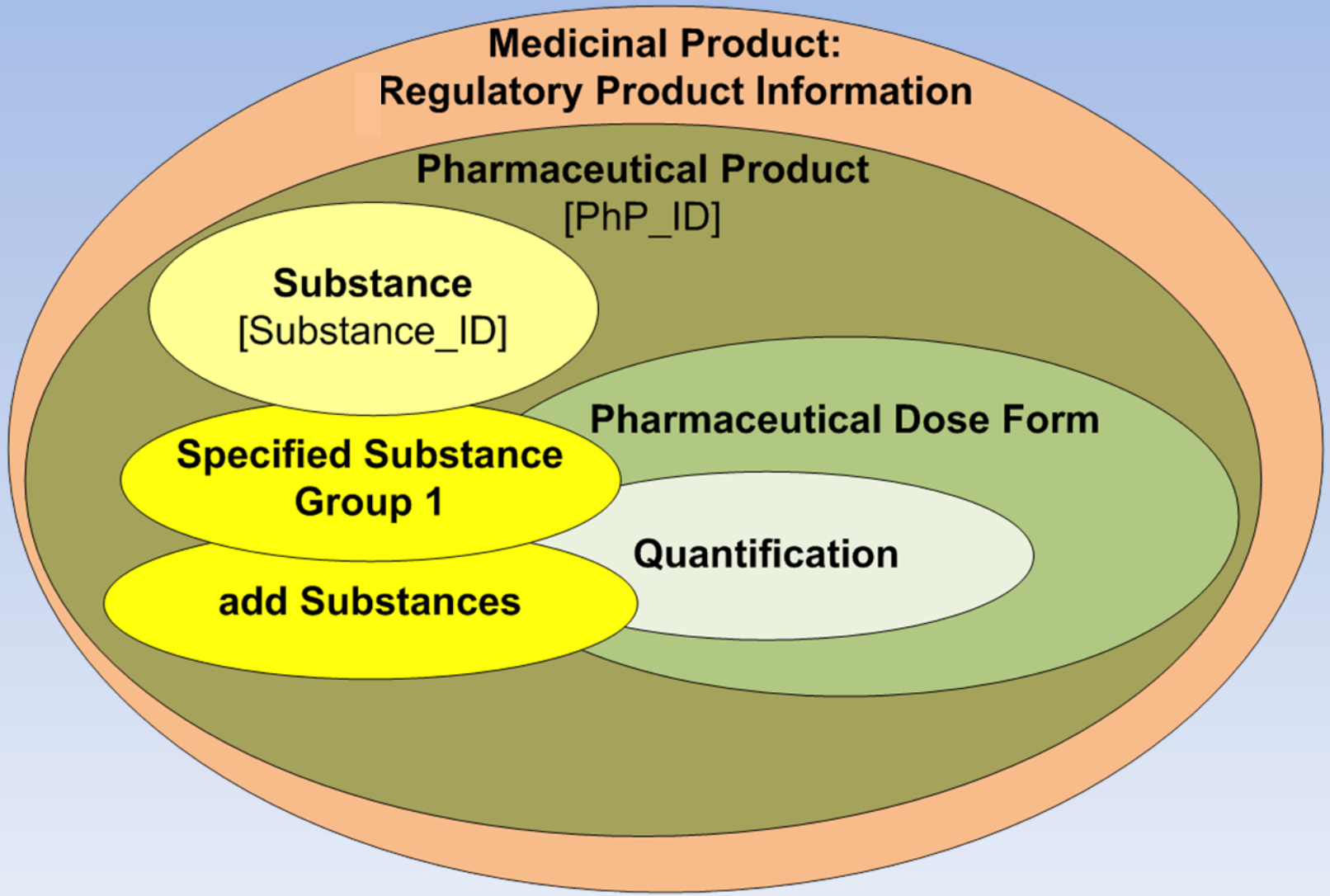
- Define
- Characterize
- Uniquely identify

regulated medicinal products for human use

Support the entire product life cycle management:

- Development
- Authorization (approval)
- Post-marketing
- Renewal or withdrawal as applicable

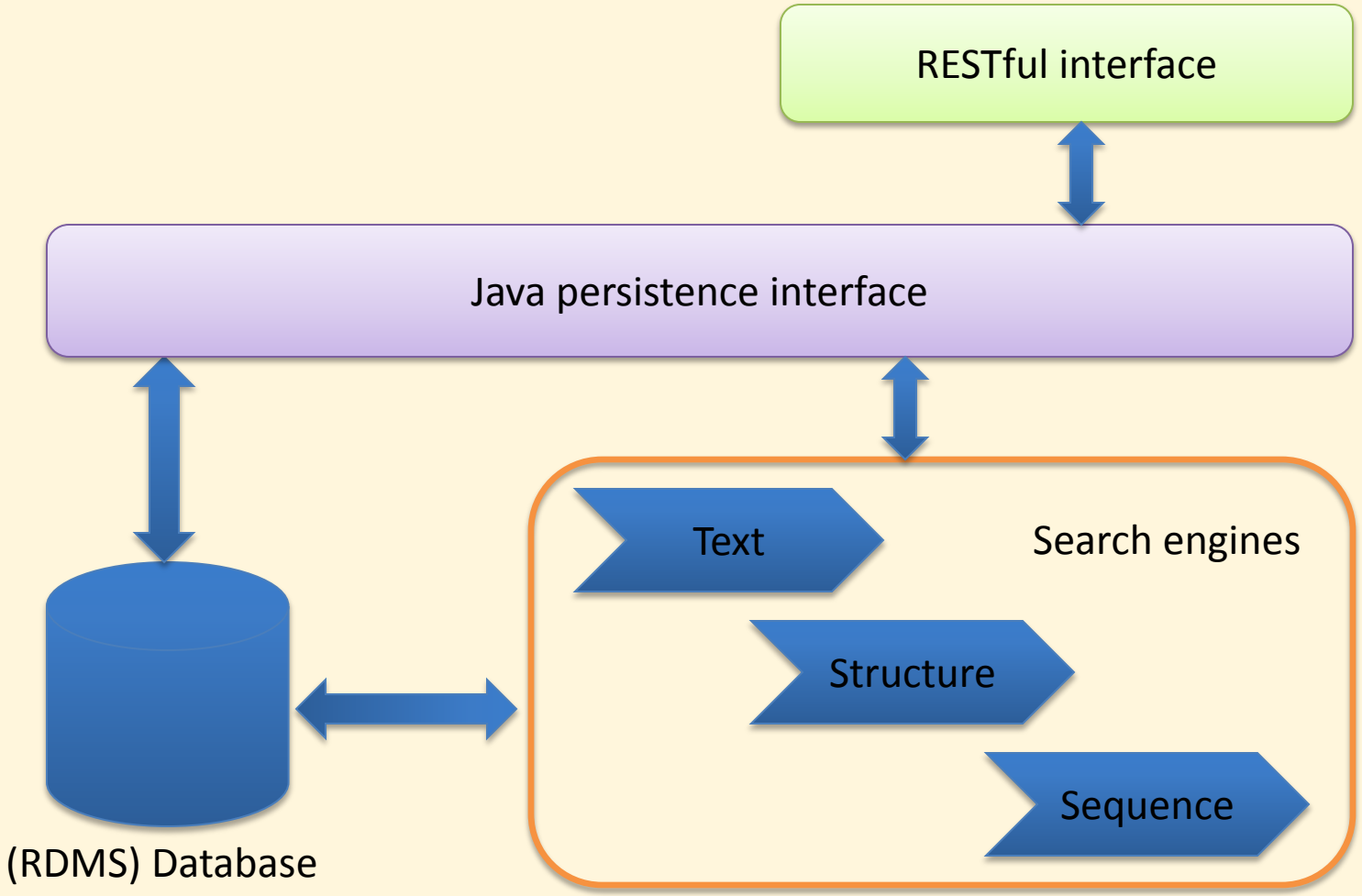
ISO-IDMP SUBSTANCE DATABASE APPROACH



ISO/IDMP 11238 Substance Standard and Scope

- Substance classes
  - Chemical
  - Protein
  - Nucleic acid
  - Polymer
  - Structurally diverse
- Specified substances Groups 1, 2, 3, 4.
- Official names in multiple languages, jurisdictions, and domains.
- Well-defined references and relationships between substances, documentation.
- Unique identifiers.

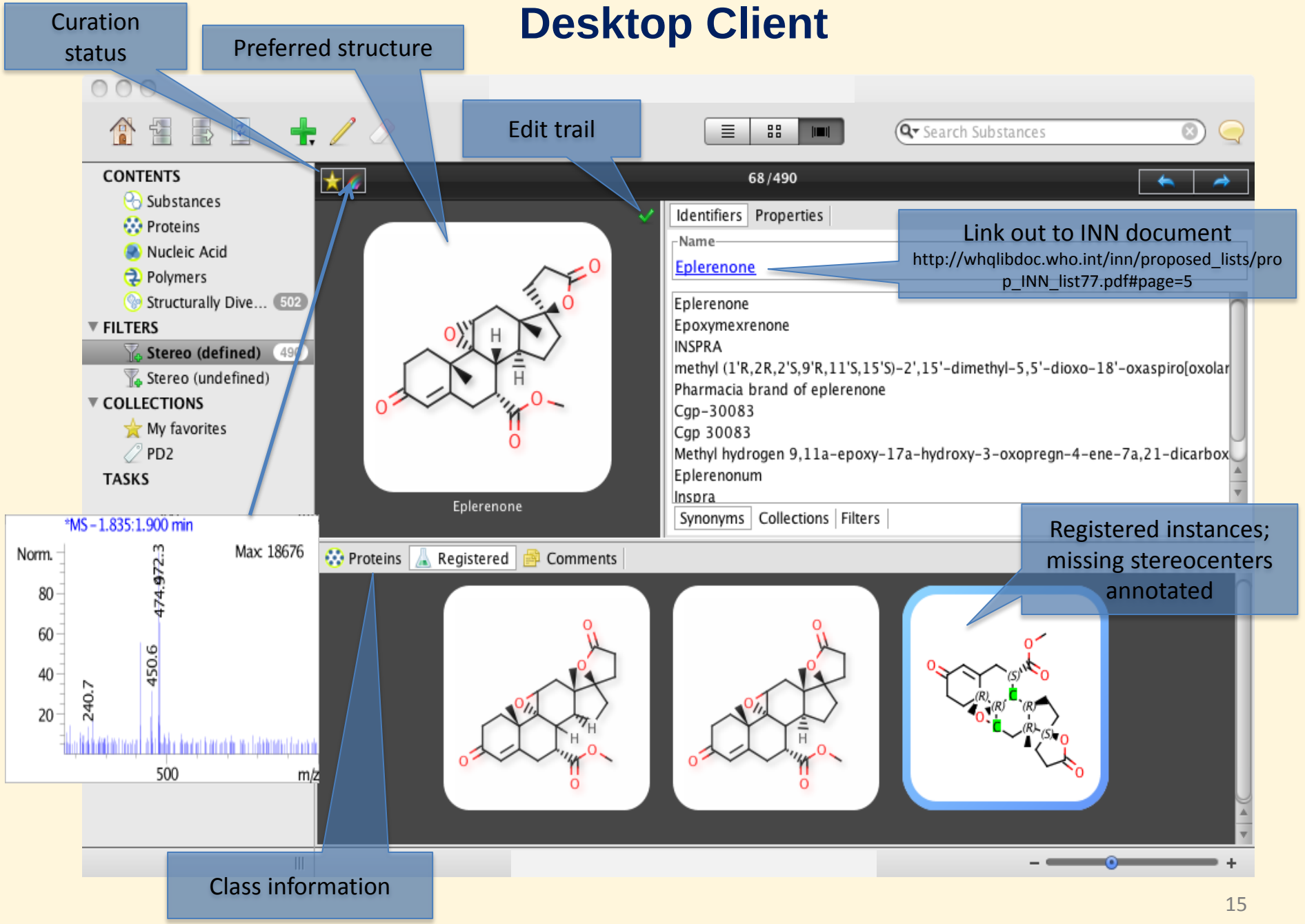
Architecture Overview



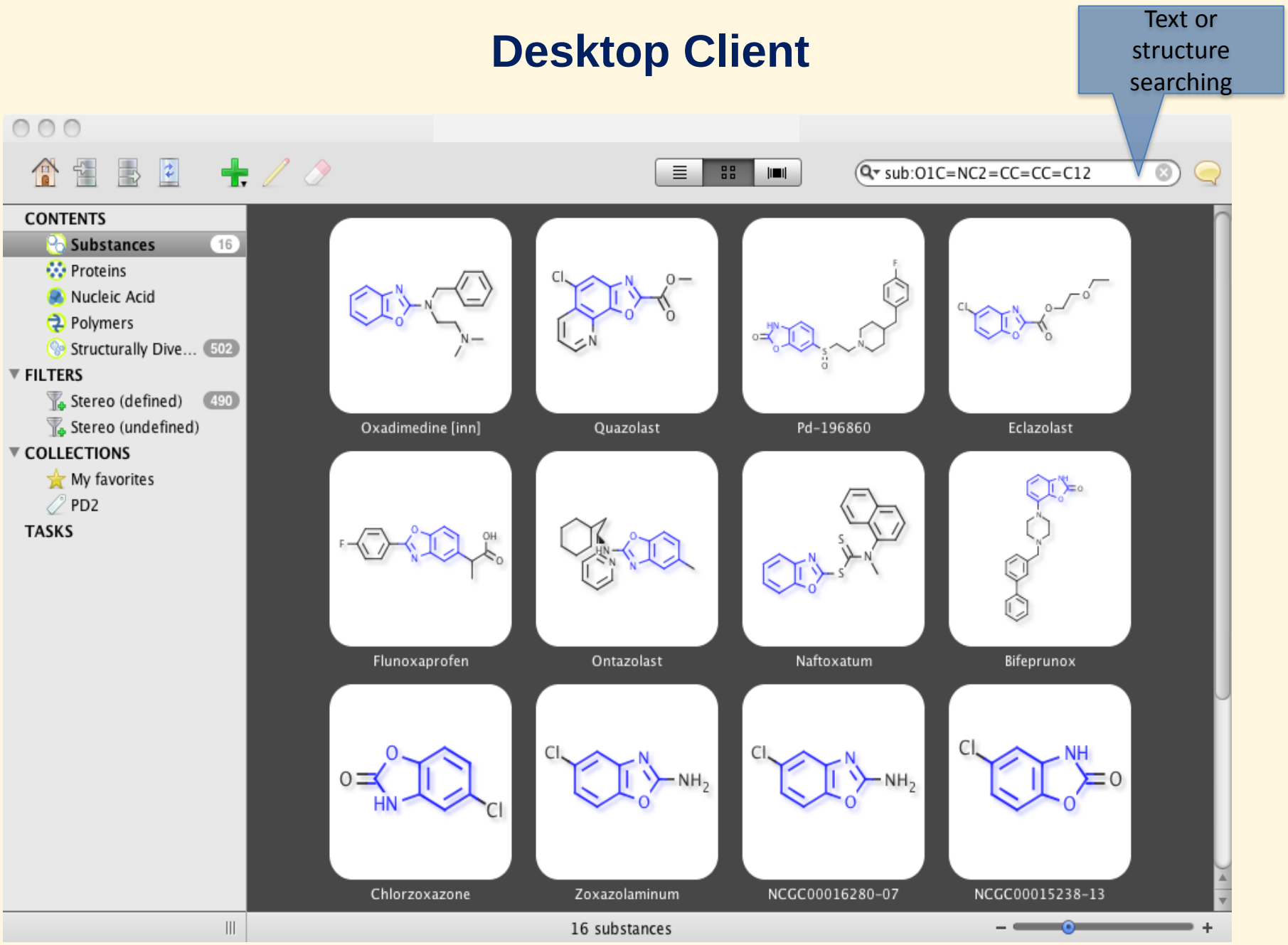
Technology Stack

- **Web-based client**
  - Combination of client- and server-side technologies (e.g., ExtJS, JSF)
- **Desktop client**
  - Java Swing and other open source libraries
  - Deploy as either signed webstart or installed image
- **Server**
  - JDO as the persistence layer
  - Lucene text search engine
  - Custom implementations of structure and sequence search engines
  - Standalone server based on embedded Jetty or Glassfish and H2 database

Desktop Client



Desktop Client



Functional Design
ISO/IDMP 11238 DATABASE

Herman Diederik and Ciska G. Matai

2013

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Definition of ISO11238 Substances

Single Substance:

A Substance that can be described by a single representation or set of descriptive elements.

Note: Racemates and substances with unknown, epimeric or mixed chirality are included.

Mixture Substance:

A Substance that is a combination of single substances isolated together or produced in the same synthetic process.

Multi Substance materials (see Group 1 Specified Substance):

Single Substances of diverse origin that are brought together and **do not** undergo a chemical transformation can be defined as multi-substance materials and not as mixture substances.

Question:

How do we classify the substance Paclitaxel-Albumin complex in the medicinal product Abraxane?

- **Answer: The product is presented as a sterile, pyrogen-free, white-to-yellow lyophilized cake formulation of nanoparticles of 100 mg paclitaxel "bound" by 800 mg human albumin.**
- **The Paclitaxel nanoparticles and the Albumin are substances of diverse origin that are brought together but do not undergo a chemical transformation.**
- **Therefore the Paclitaxel – Albumin complex can be defined as multi-substance materials and are placed in accordance with the standard in**

Specified Substance Group 1.

Question:

How do we classify the complex VEMURAFENIB non crystalline co-precipitate with Hypromellose acetate succinate (30 : 70)?

Answer: **The Vemurafenib-HPMC-AS polymer co-precipitate/ complex complies with the ISO-IDMP 11238 definition for "Mixture Substance" :"A Substance that is a combination of single substances isolated together or produced in the same synthetic process" So that:**

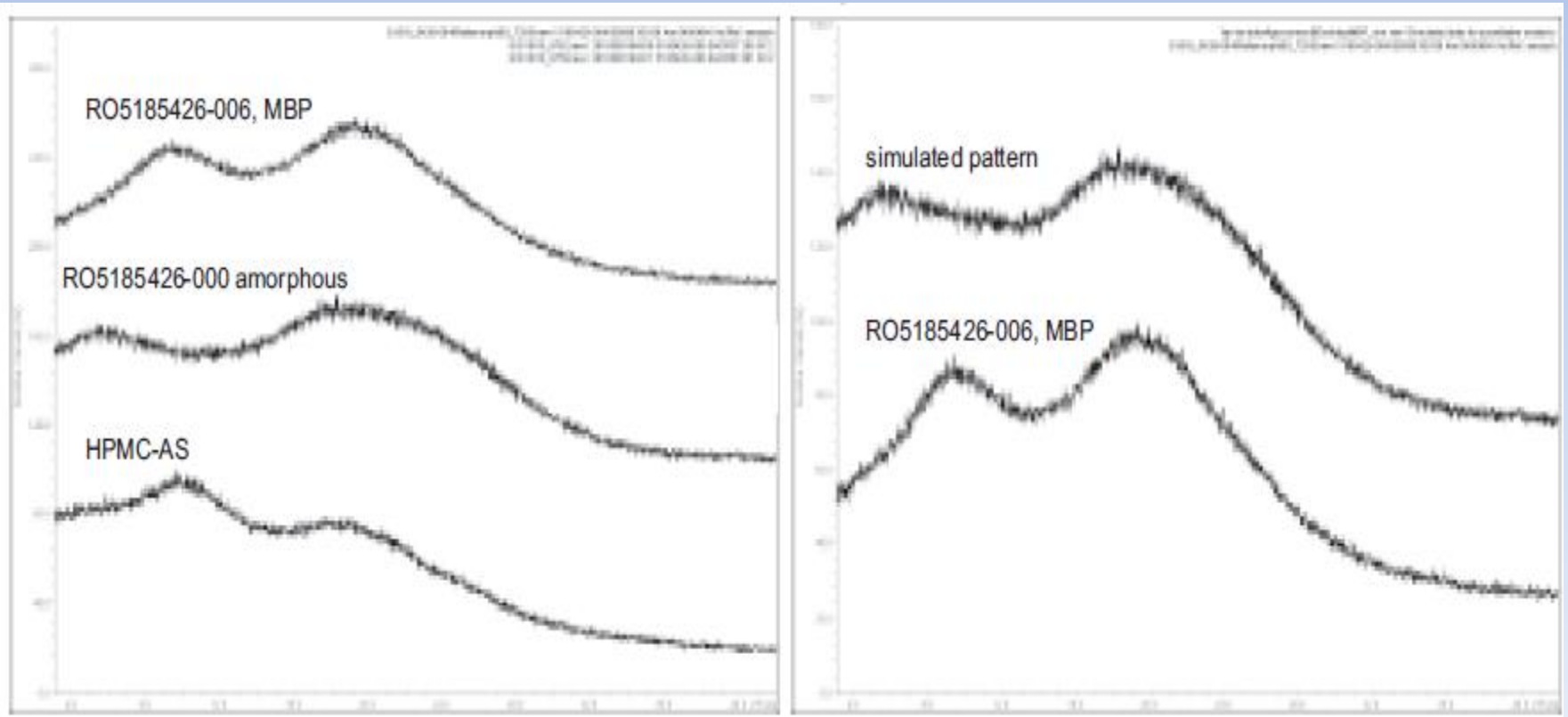
A: Vemurafenib is the parent substance name and Vemurafenib, polymorph crystalline form II, is the Specified parent substance group 1 name;

B: Vemurafenib-HPMC-AS-polymer (co-precipitate or complex is to be considered as the related "child" substance.

[Note: Both Vemurafenib and HPMC-AS are dissolved in DMA at 80^{o}C. After mixing with cold aqueous diluted HCL (0-7^{o}C) Vemurafenib and HMPC-AS (co)-precipitate. The co-precipitate is washed, dried and milled and has a distinct XRPD-pattern from the individual components and from the simulated physical mixture of individual components.]

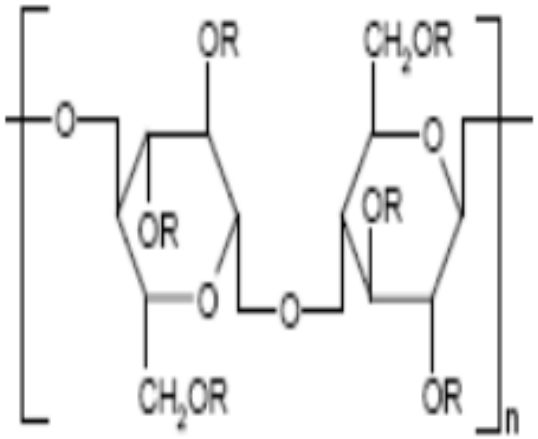
Left: **Overlay of XRPD patterns of HPMC-AS, amorphous Vemurafenib (RO5185426-000) and Vemurafenib-Hypromellose Acetate Succinate(RO5185426006 (MBP)**

Right: **Simulated pattern (Least squares fit) and experimental pattern physical mixture**



Specification of Polymer
Hydroxypropyl Methylcellulose Acetate Succinate

Hydroxypropyl methylcellulose acetate succinate



R= -H
-CH_3
-$CH_2CH(CH_3)OH$
-$COCH_3$
-$COCH_2CH_2COOH$
-$CH_2CH(CH_3)OCOCH_3$
-$CH_2CH(CH_3)OCOCH_2CH_2COOH$

Appearance: granulated powder
Color: white to yellowish white
Identity (ATR-IR or IR): corresponds
Viscosity (2% sol in 0.43% NaOH at 20 °C): 2.4 – 3.6 mm^2/s
Loss on drying: max. 1.5%
Sulphated ash: max. 0.20%
Heavy metals (Ph.Eur. Method A or XRF): max. 10 ppm.

Free acids (as acetic and succinic acids, HPLC): max. 1.0%

Content of acetyl groups (dried, HPLC): 5.0 – 9.0%

Content of succinoyl groups (dried, HPLC): 14.0 – 18.0%

Content of methoxy groups (dried, GC): 20.0 – 24.0%

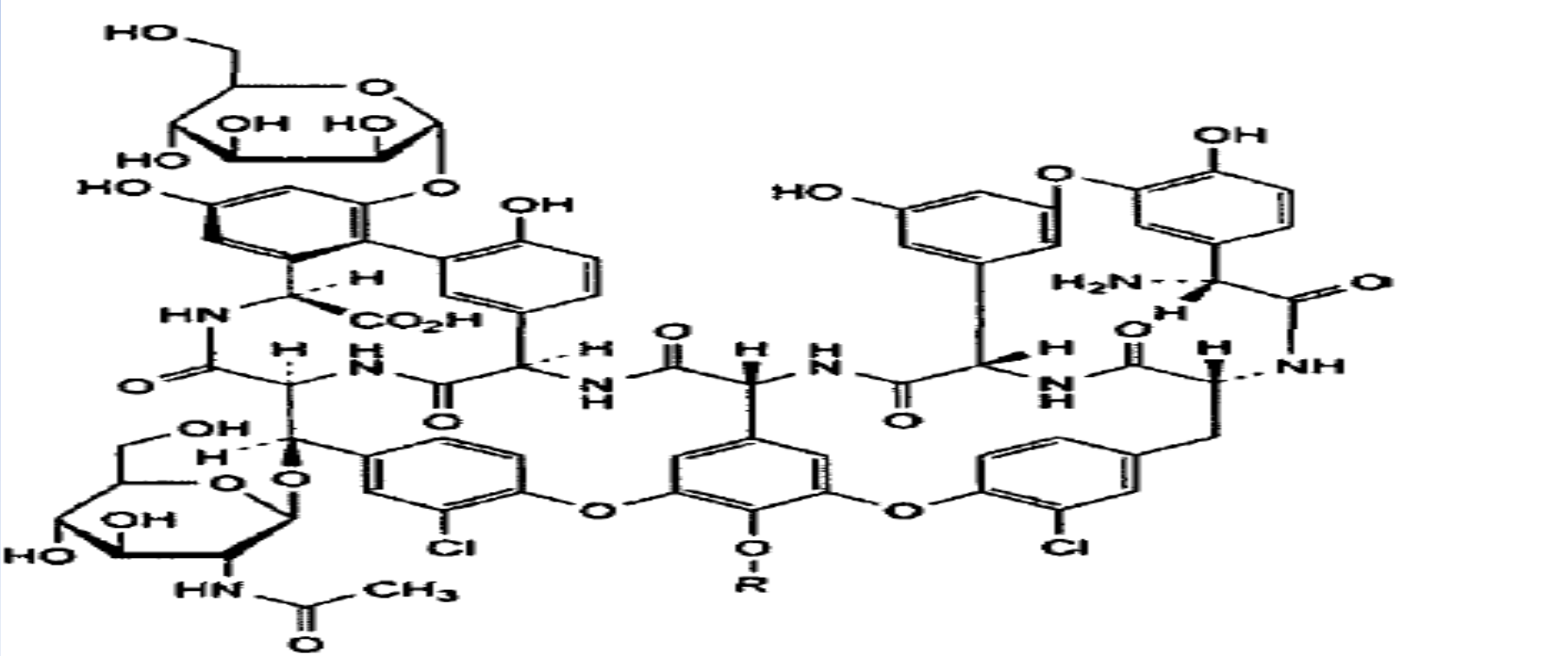
Content of hydroxypropoxy groups (dried, GC): 5.0 – 9.0%
Residual solvents (GC): passes test, complies with USP and Ph.Eur.

Question: **What is the classification of Teicoplanin according to the ISO-IDMP-11238 Standard.**

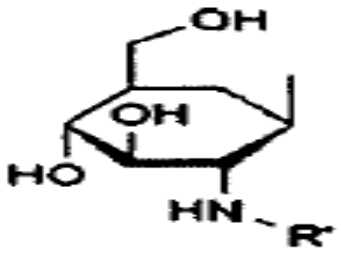
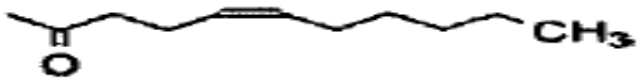
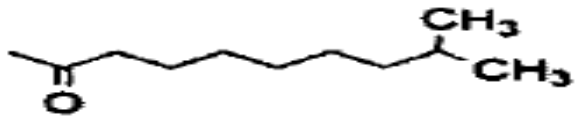
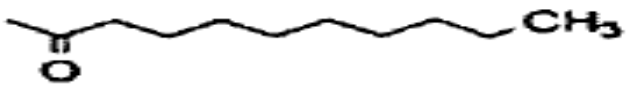
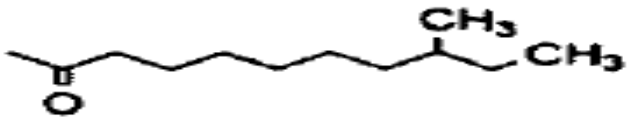
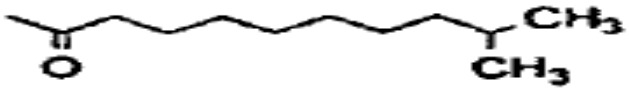
DEFINITION: Mixture of glycopeptides produced by certain strains of Actinoplanes teichomyceticus sp. ; the 6 principal components of the mixture are teicoplanin A2-1 to A2-5 and teicoplanin A3. It is a fermentation product.

The chemical structure consists of 6 components of glycopeptides, which are composed of a hepta-peptide core of 7 amino acids connected with 3 sugars .

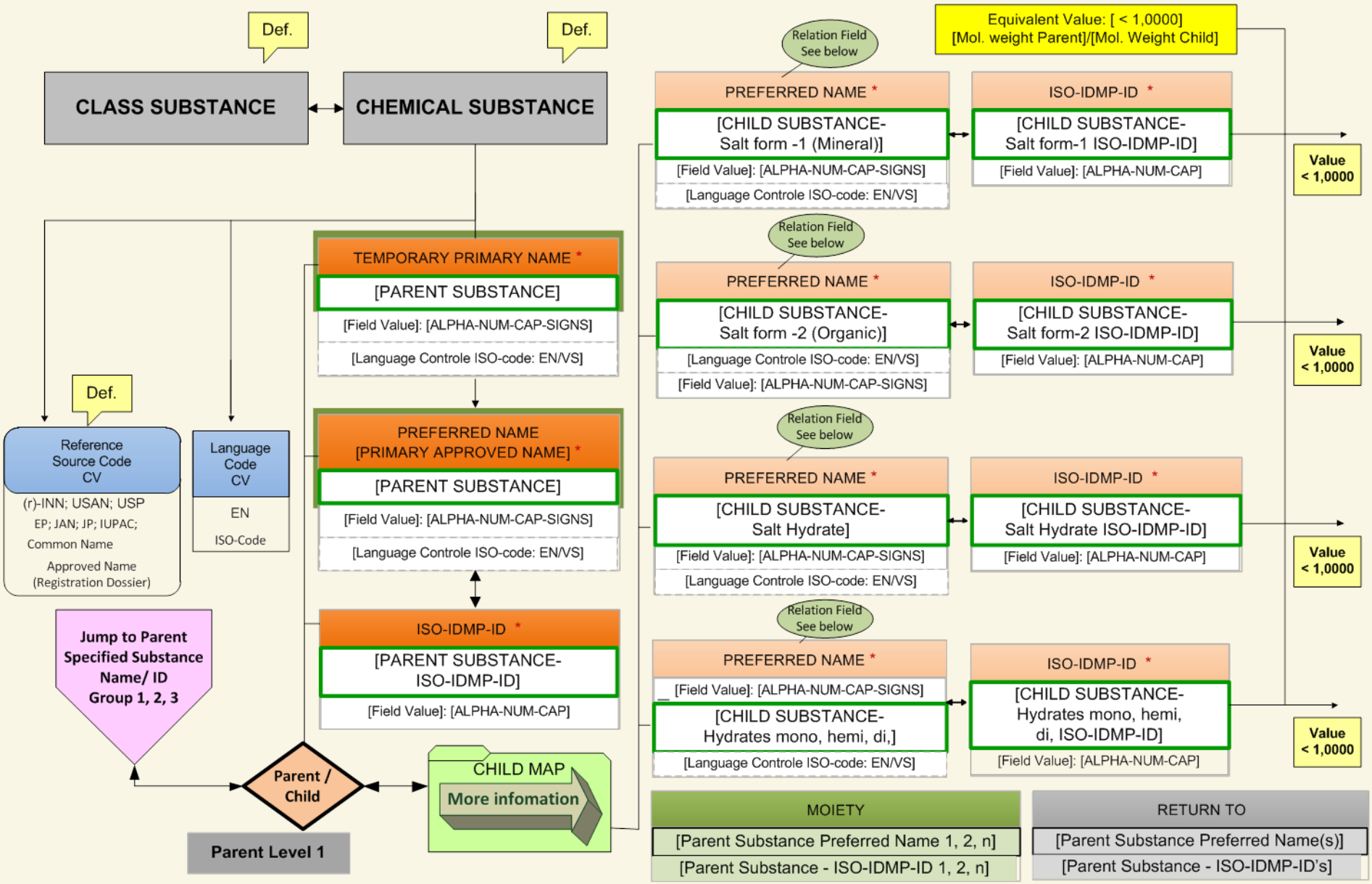
(N-acetylglucosamine, α-mannitose and the glucose substituted by different N-acylamino).



Answer: **The substance is a mixture of components isolated together** (or produced in the same synthetic process). **Conclusion: The substance Teicoplanin will be classified as a Mixture substance, having a Parent Substance ISO-IDMP-ID.**

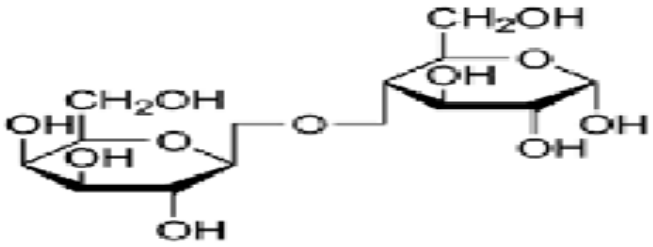
Teicoplanin	R	R'
A_{2-1} $C_{88}H_{95}Cl_2N_9O_{33}$ M. W.: 1878		
A_{2-2} $C_{88}H_{97}Cl_2N_9O_{33}$ M. W.: 1880		
A_{2-3} $C_{88}H_{97}Cl_2N_9O_{33}$ M. W.: 1880		
A_{2-4} $C_{89}H_{99}Cl_2N_9O_{33}$ M. W.: 1894		
A_{2-5} $C_{89}H_{99}Cl_2N_9O_{33}$ M. W.: 1894		
A_{3-1} $C_{72}H_{68}Cl_2N_8O_{28}$ M. W.: 1564	H	

Layer 0 [Chemical Substance]

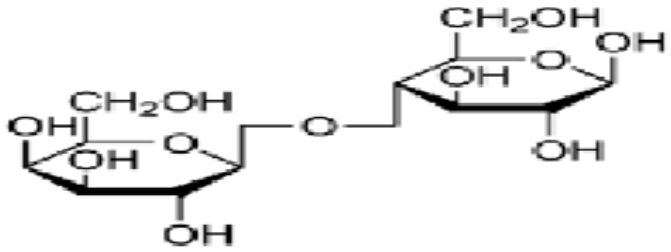


Lactose anhydrous consist of:

(β-D-Galactose) (α-D-Glucose) (β-D-Galactose) (β-D-Glucose)



Anhydrous α-lactose



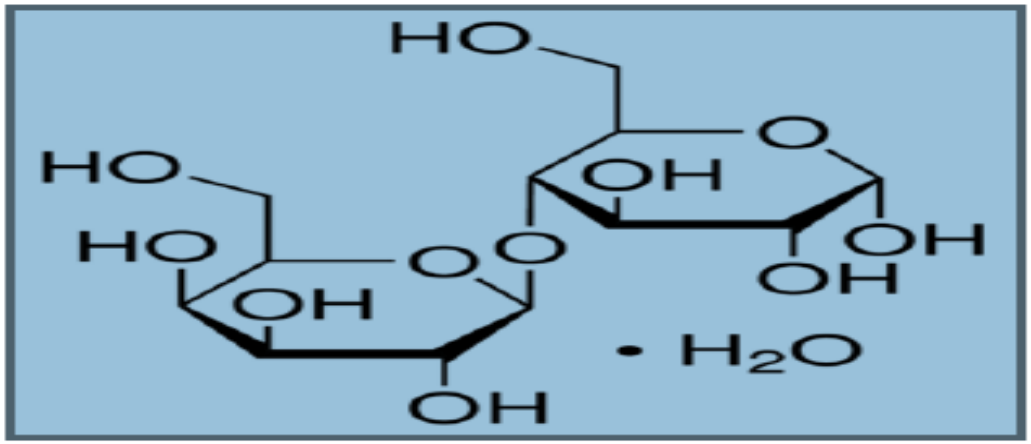
Anhydrous β-lactose

The PhEur 7.4 and USP35–NF30 describe anhydrous lactose as *O*-β-D-galactopyranosyl-(1 to 4)-β-D-glucopyranose; or as a mixture of

***O*-β-D-galactopyranosyl-(1 to 4)-β-D-glucopyranose and *O*-β-D-galactopyranosyl-(1 to 4)-α-D-glucopyranose.**

Definition: Lactose monohydrate is the monohydrate of *O*-β-D-galactopyranosyl-(1 to 4)-α-D-glucopyranose

Synonym: D-(+) Lactose monohydrate (99,0%) or α-Lactose monohydrate.



CLASSIFICATION SUBSTANCE ISO-IDMP-DATABASE LAYER DEFINITION

Layer 0.0: FLOW CHART CHEMICAL SUBSTANCE

Layer 0 [Chemical Substance] PREFERRED NAME and ISO-IDMP-ID (*Parent Substance*)

Parent/ Child Specified Substance Name/ ID Group 1, 2, 3

Child Substance Name/ ID and Equivalent Value *Child Substance/ Parent Substance*

Layer 1 [Chemical Substance] [Naming and Coding of *Parent/ Child Substance*]

Layer 2 [Chemical Substance] [Molecular Formula, Molecular Weight, Molecular Structure] [*Parent/ Child Substance*]

Chemical Substance Role Classification of Isomers/ Impurities/ Degradant/ etc:

Chemical Name (*Parent Substance* and Structurally Related Substance; Molecular Structure an Molecular Weight

Layer 3 [Chemical Substance] [Naming and Coding of *Parent/ Child Substance*] ***Specified Substance Group 1***

Parent/ Child Substance Specified Substance Group 1 **Constituents** (Name and ISO-IDMP-ID)

Constituent Role and Properties/ Notes Field

Definition of ISO11238 Specified Substances

- **Specified Substance: Group 1:**
  Multi-substance materials; constituents, (marker substance and extraction solvents for herbals and allergenic extracts), physical form and any physical property that is essential for defining the specified substance. i.e. grade

- **Specified Substance: Group 2:**
  Limited manufacturing information; parent substance or group 1 specified substance (and ID's), manufacturer, high level production method: overall production method type, (i.e. synthetic, extractive, recombinant) production system type, (i.e. cell line, plant or animal tissue), production system (specific cell line).

- **Specified Substance: Group 3:**
  Parent substance or group 1 specified substance (and ID's), source and other properties.

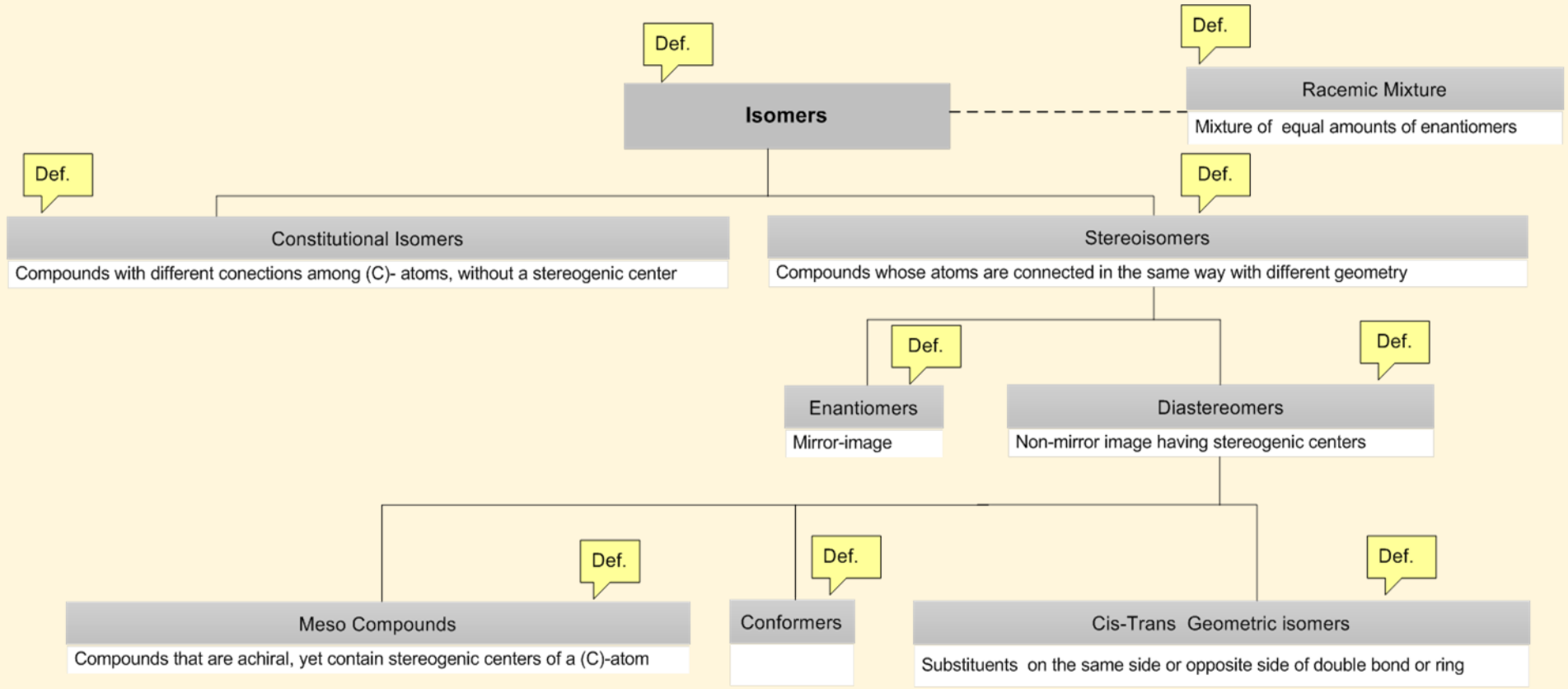
- **Specified Substance: Group 4:**
  Detailed manufacturing information, constituents (impurities, degradents which are not captured in Group 1), and specifications.

Layer 2 [Chemical Substance]

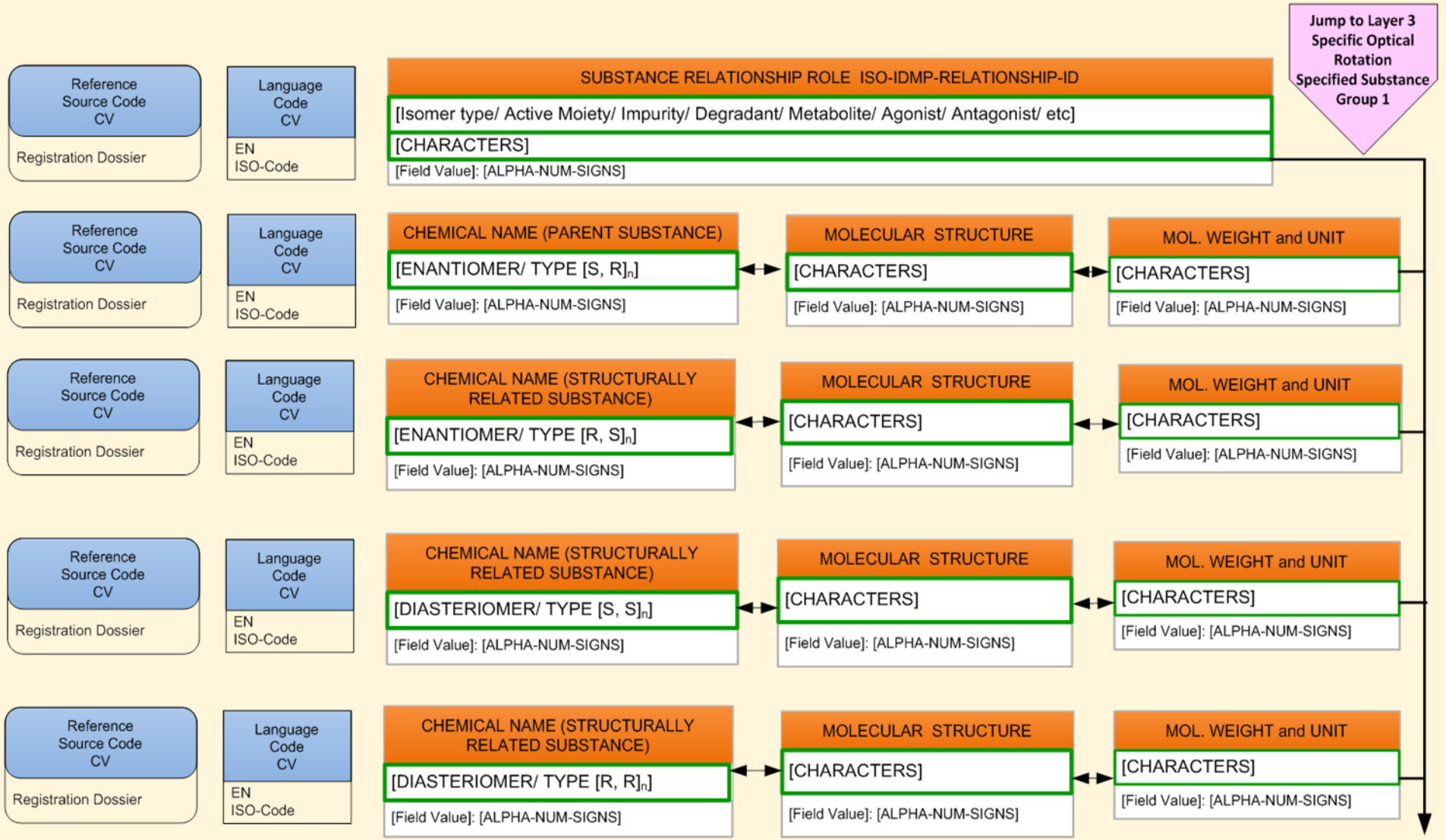
Layer 2 [Naming and Coding of Parent Substance or Child Active Moiety Structural Relationship]

Preferred Name Parent Substance	ISO-IDMP-ID Parent Substance-ISO-IDMP-ID	Preferred Name Child Substance Active Moiety	ISO-IDMP-RELATIONSHIP-ID Child Substance Active Moiety

Classification of Isomers



Layer 2 [Naming and Coding of Parent Substance or Child Active Moiety Structural Relationship] *continue*



CLASSIFICATION SUBSTANCE ISO-IDMP-DATABASE LAYER DEFINITION *continue*

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Layer 6 [*Parent/ Child Substance*] **Documentation**

Public Domain

Restricted Domain Part I
(Competent Registration Authority Only)

Restricted Domain Part II
(Competent Registration Authority, Editorial Reviewer Only)

↓

Layer 7 [Chemical Substance] **LEGEND**

MANDATORY SOURCES
What do we understand with a “Common Name”

The information on the nomenclature of a substance should be provided, if relevant by:

- **International Nonproprietary Name (INN) or Recommended INN assigned by the WHO.**
- Substances not covered by INNs:

  mixtures of substances; substances not completely characterized; herbal substances; substances having a well-established name (alkaloids).

- **Compendial Name (Official Name)**:

  e.g.European Pharmacopoeia (EP); United States Pharmacopoeia (USP).
- **National Approved Names**:
  BAN, USAN, JAN, Company or Laboratory code
- **Systematic Chemical Name(s)** (IUPAC nomenclature)
- **Other Names** (e.g. Proprietary) and Other non-proprietary name(s)
- **Chemical Abstract Service (CAS) registry name, e.g. CAS-Index name**

PREFERRED NAME:

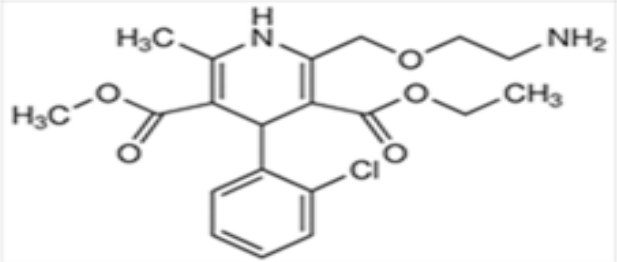
USP: AMLODIPINE BESYLATE; EP: AMLODIPINE BESILATE;

INN: Amlodipini Besilas [rINNM (la)

INN: Amlodipine Besilate [rINNM (en)]

INN: Besilato de amlodipino [rINNM (es)]

INN: Амлодипина Безилат [rINNM (ru)]



CHEMICAL NAME:

CAS: **3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, benzenesulfonate (1:1) (CA INDEX NAME)**

USP: **3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, monobenzenesulfonate.**

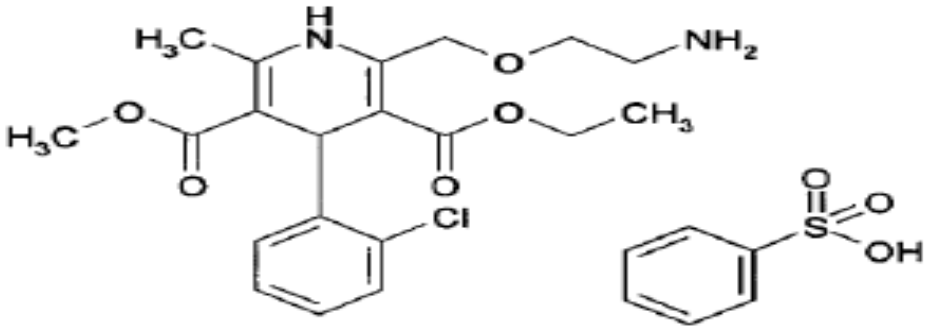
EP: **3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-l,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate.**

Martindale Parent Substance AMLODIPINE:

3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate

APPLICANT:

- Structural formula:



- Molecular formula: $C_{20}H_{25}ClN_2O_5$, $C_6H_6O_3S$

- Relative molecular mass: 567.1 (408.882 + 158.178)
  The conversion factor for the salt to the base is 0.721.

- Amlodipine corresponds to the racemic mixture (one asymmetric carbon).

MOLECULAR FORMULA/ Weight:

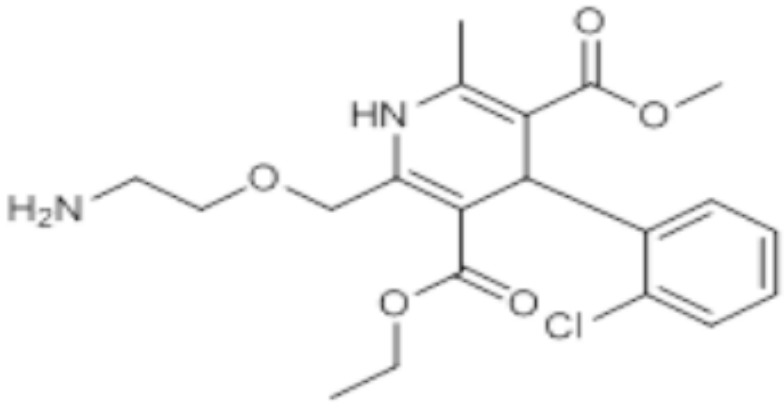
USP: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$; 567.05

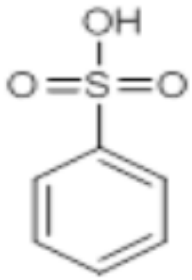
EP: $C_{26}H_{31}ClN_2O_8S$; 567,1

CAS: C20 H25 Cl N2 05 . C6 H6 03 S; No presentation of Mol. Weight.

Martindale: $C_{20}H_{25}ClN_2O_5, C_6H_6O_3S$ =567.0

Case study Amlodipine Besylate





Official Name
Salt / Parent Relationship
Approved Drug
Chemical Substance

Implementation of

ISO/IDMP 11238 Substance Standard and Movement towards a Global Ingredient Archival System

GInAS

Herman Diederik and Ciska G. Matai, CBG-MEB
Thomas Balzer, BfArM
Vikesh Srivastava, Health Canada
Larry Callahan, Frank Switzer, FDA
Tyler Peryea, Trung Nguyen and Noel Southall, NCATS
Phillipp Weyermann, SwissMedic

February - September, 2013

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Functional Design
ISO/IDMP 11238 DATABASE

Herman Diederik and Ciska G. Matai

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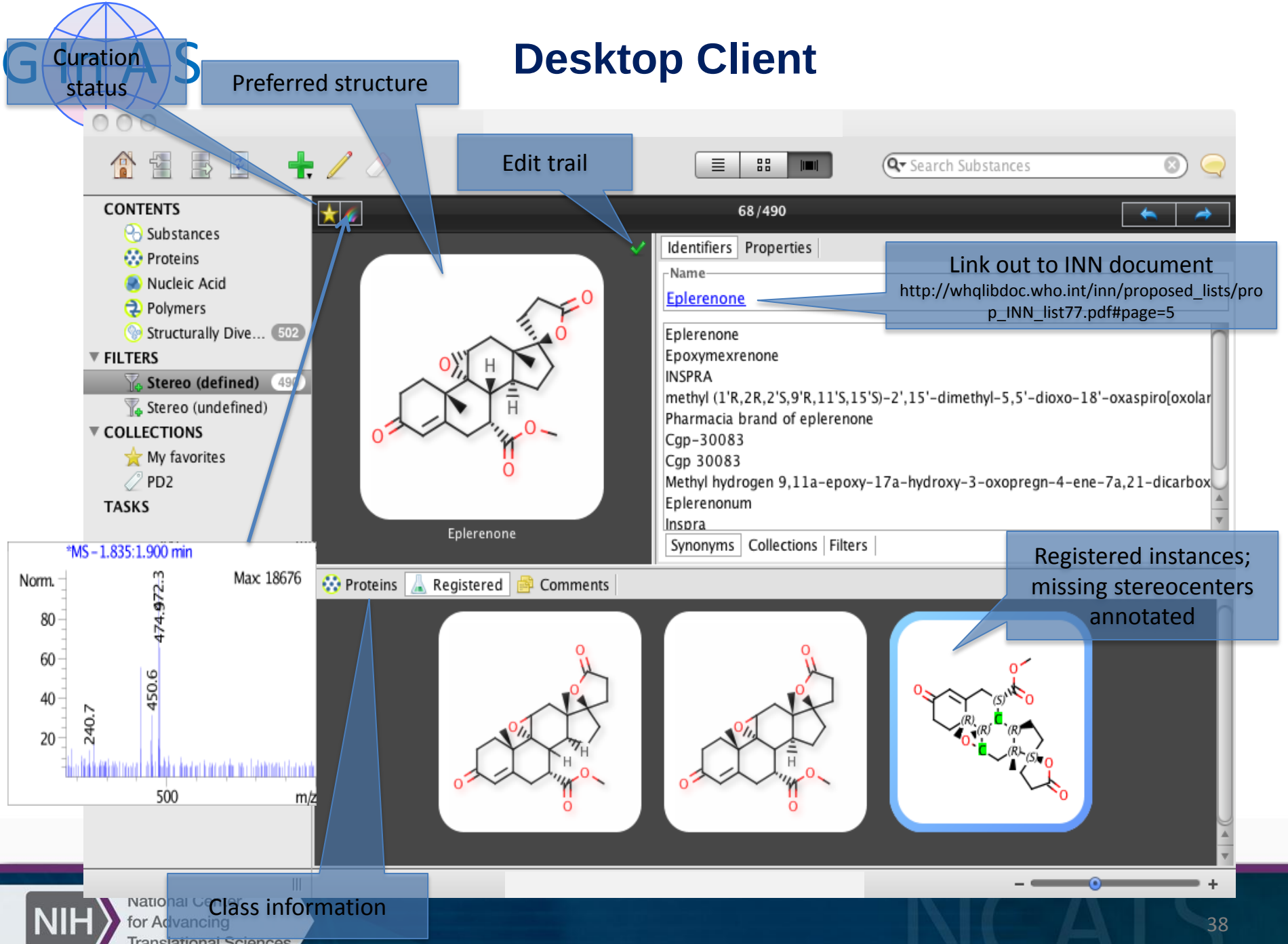
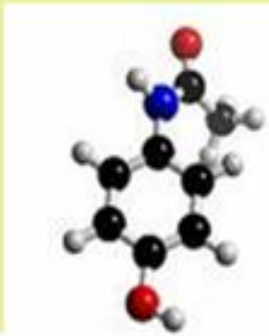


For Non-Stoichiometric Composed Substances and Biological Substances more elements has to be captured:

- Biological medicines produced in a living system or organism
- The (complex) manufacturing process is a determining factor

- Larger molecules, complex (three-dimensional structure) and heterogeneous (e.g. isoforms and multimers)
- Difficult to characterise
- Impurities: Both Product-related and Process-related
- Low stability



Substance Class: Peptide/ Proteins; **Linaclotide**

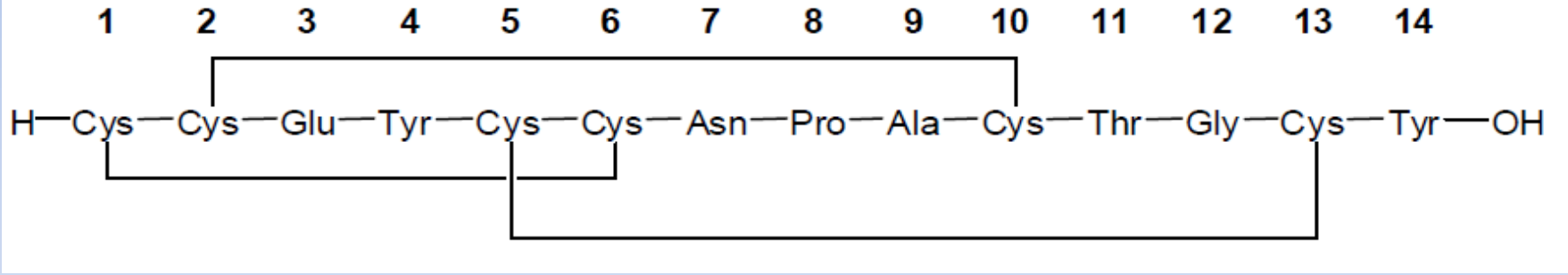
WHO Drug Information, Vol. 21, No 3, 2007; Rec INN: List 58.

Names: INN: Linaclotidum; Linaclotide:

Linaclotide [9-L-tyrosine]heat-stable entetotoxin (*Escherichia coli*)-(6-19);

CAS-Name: L-Tyrosine, L-cysteinyl-L-cysteinyl-L-.alpha.-glutamyl-L-tyrosyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-threonylglycyl-L-cysteinyl-, cyclic (1↔6),(2 ↔10),(5 ↔13)-tris(disulfide); **Cas Number:** 851199-59-2

Figure 1: Chemical structure of linaclotide



Structure: Linaclotide is a 14 AA synthetic peptide with 3 disulfide bridges.

All Amino Acids are of L-configuration.; Sequence: **1 CCEYCCNPAC TGCY;**

Formula: C59 H79 N 15 O21 S6; Mol. Weight: 1.526,8 Da.

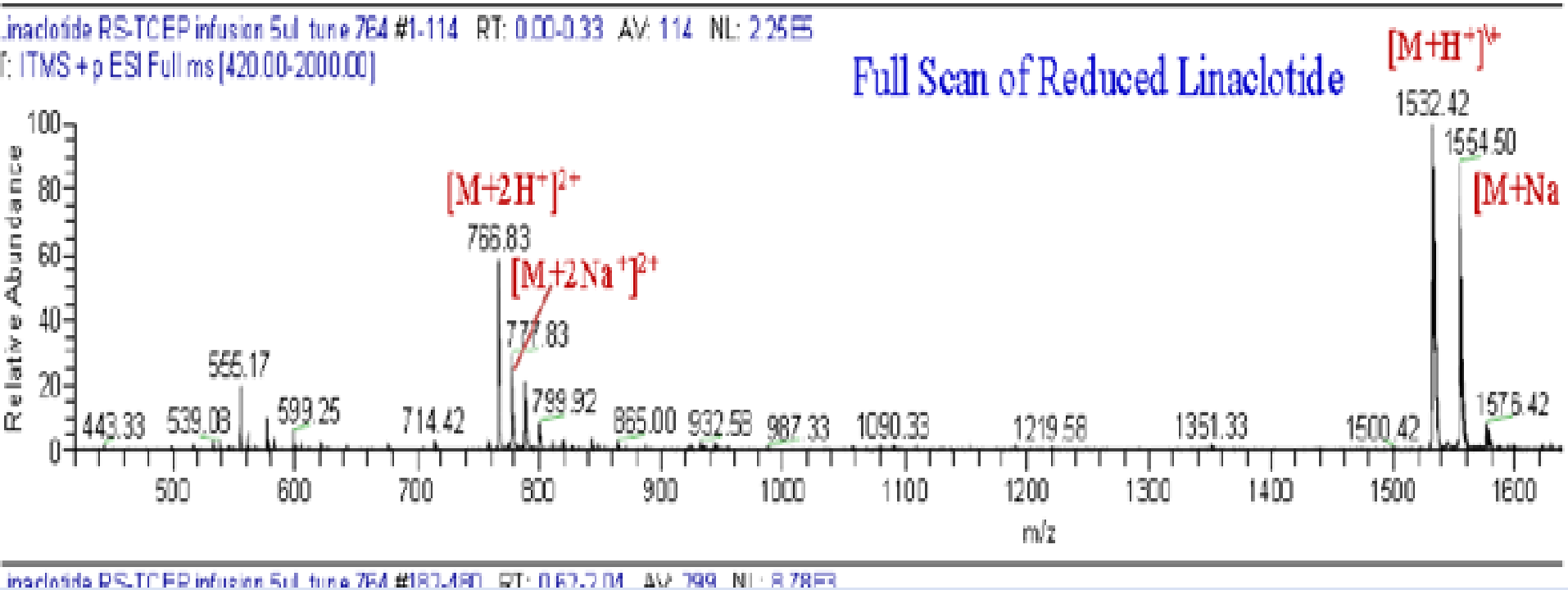
Description: Amorphous, white powder, (No XRPD patterns), soluble in water;

Physical properties: pH (2,4 mg/ml = 3.4) ; pK-values; Isoelectric Point = 4,0;

Specific optical rotation: -235^{0} to -261° (589 nm, c = 0,1 in 1% Acetic Acid)

Linaclotide
Characterization of Structure by ES+/MS-sequencing

Reduced disulfide bonds of Linaclotide was obtained by tris(2-carboxyethyl)phosphine (TCEP) sufficient M2 fragments were obtained.

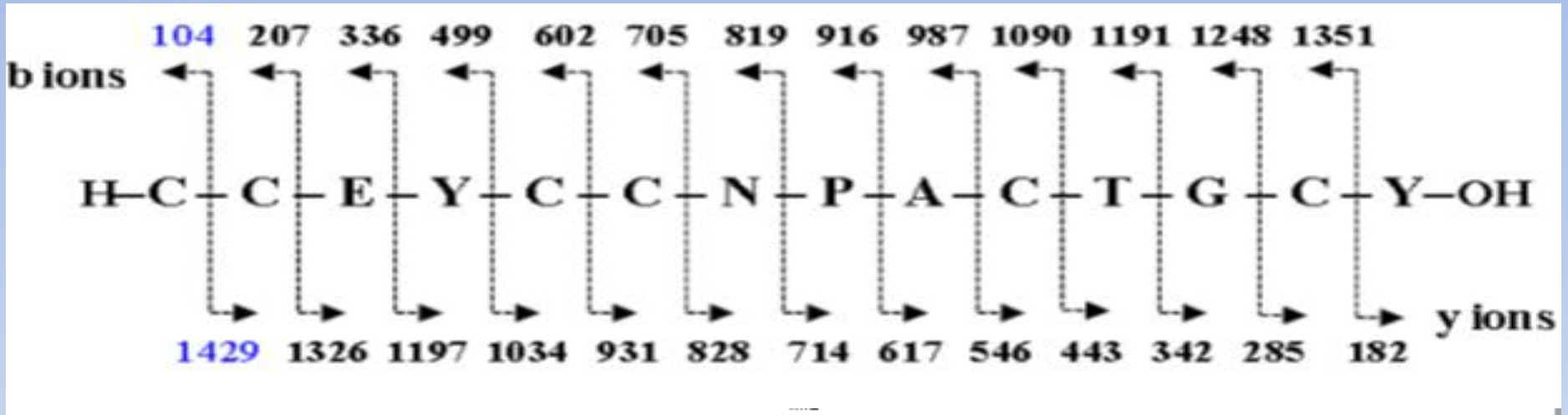


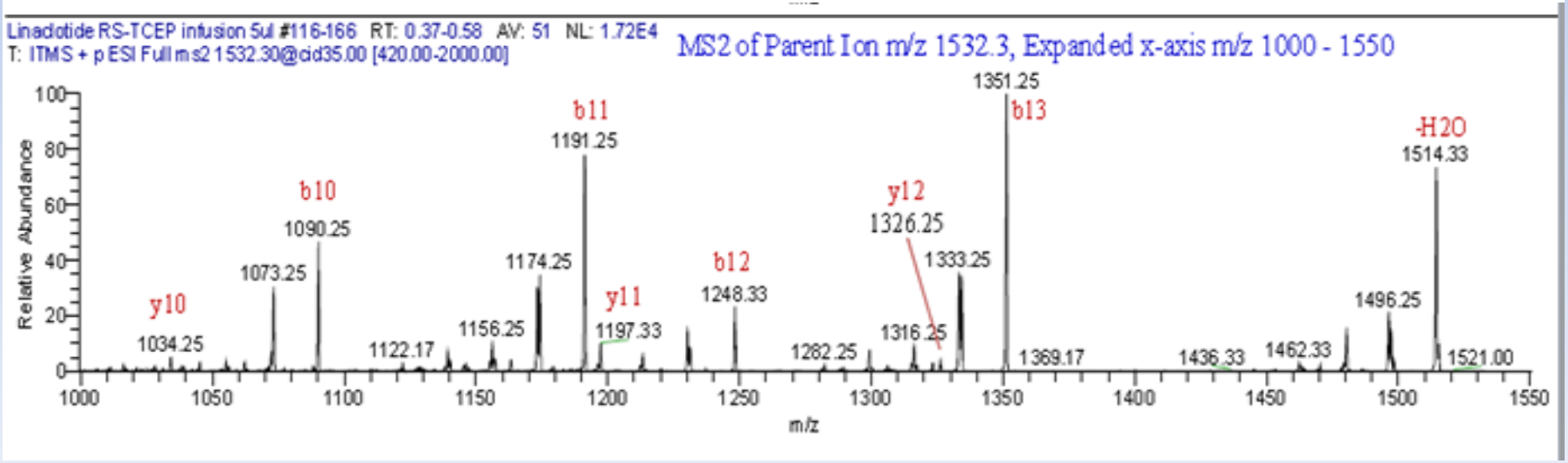
Mol. Weight of Reduced Linaclotide: 1.526,4 + 6H = 1.532,4;

Linaclotide

Characterization of Structure by ES+/MS-sequencing

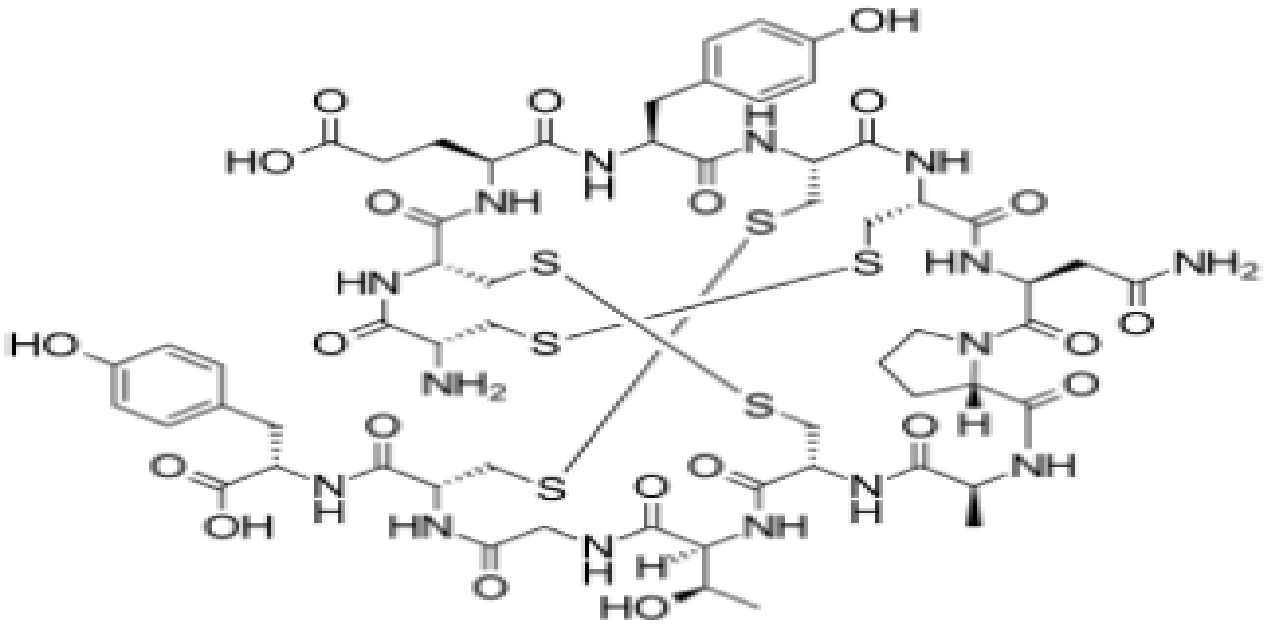
MS2 and MS3 fragments (b and y Ions) obtained of reduced Linaclotide





Case Study Linaclotide

Linaclotide



New Peptide
New Protein
New Substance
Amino Acid Sequence

Substance Class: Peptide/ Proteins;
Insulin Degludec

WHO Drug Information, Vol. 24, No 1, 2010; Rec INN: List 63.

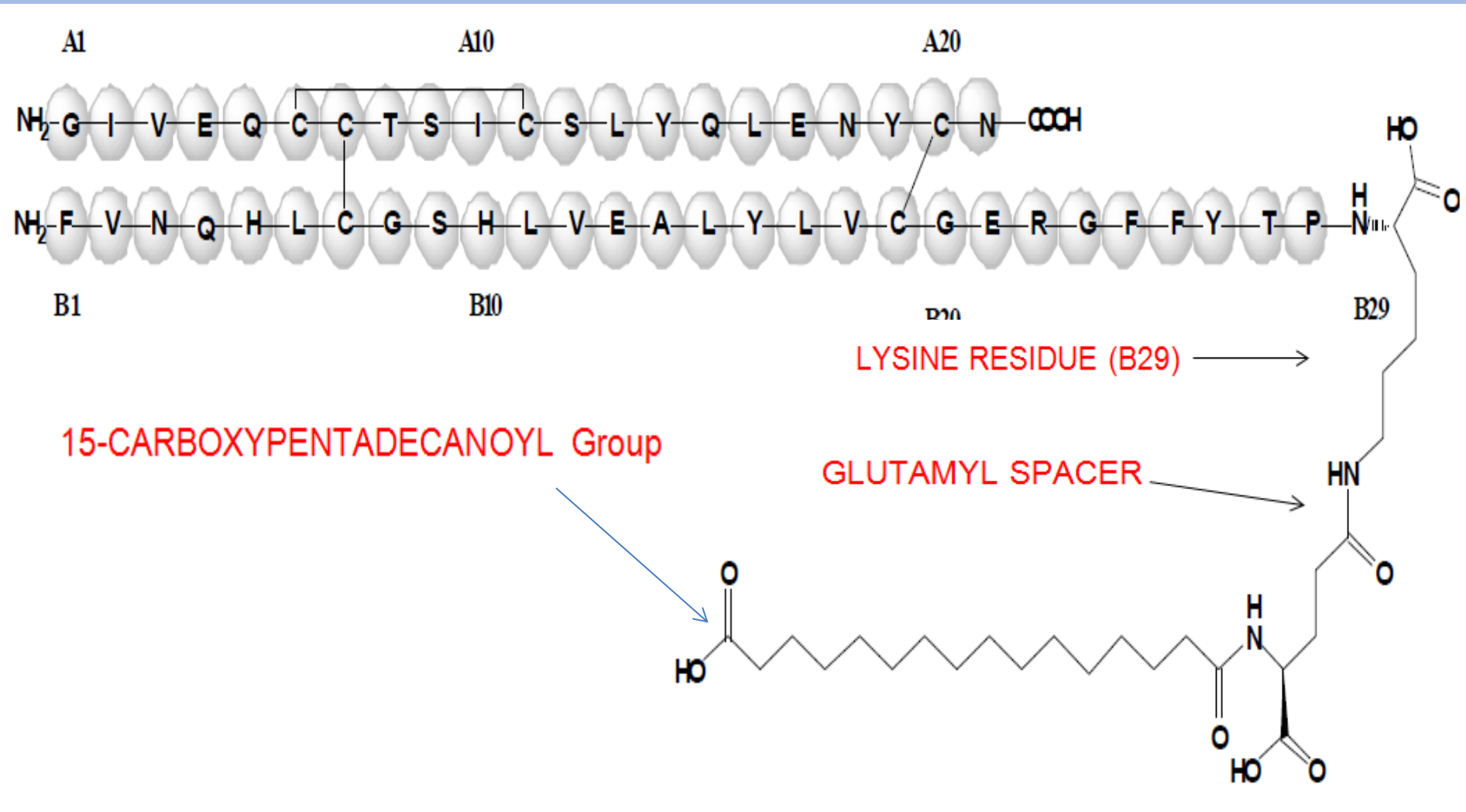
NAMES: INN: Insulinum degludecum; Insulin degludec.

- **Chemical name:**
  *N*6, B29-[*N*2-(15-carboxypentadecanoyl)-L-y-glutamyl]-des-B30-L-threonine-insulin human;
- **Description:** Insulin Degludec is a recombinant human insulin analog acylated with hexadecanedioic acid via a spacer of glutamic acid to the e-amino group of lysine residue at position 29 of B-chain, lacking threonine at position 30 of B-chain.
- Insulin Degludec is a modified two chain peptide:
  A chain 21 amino acids; B chain 29 amino acids residues;
- **Mol. Weight: 6.103,9 Da; Mo. Formula: C274 H411 N65 O81 S6**
- **Insulin degludec is produced by recombinant DNA technology in the yeast** *Saccharomyces cerevisiae.*

  [Fermentation of Precursor Insulin; Recovery of des B30 Insulin; Chemical modification; Purification]

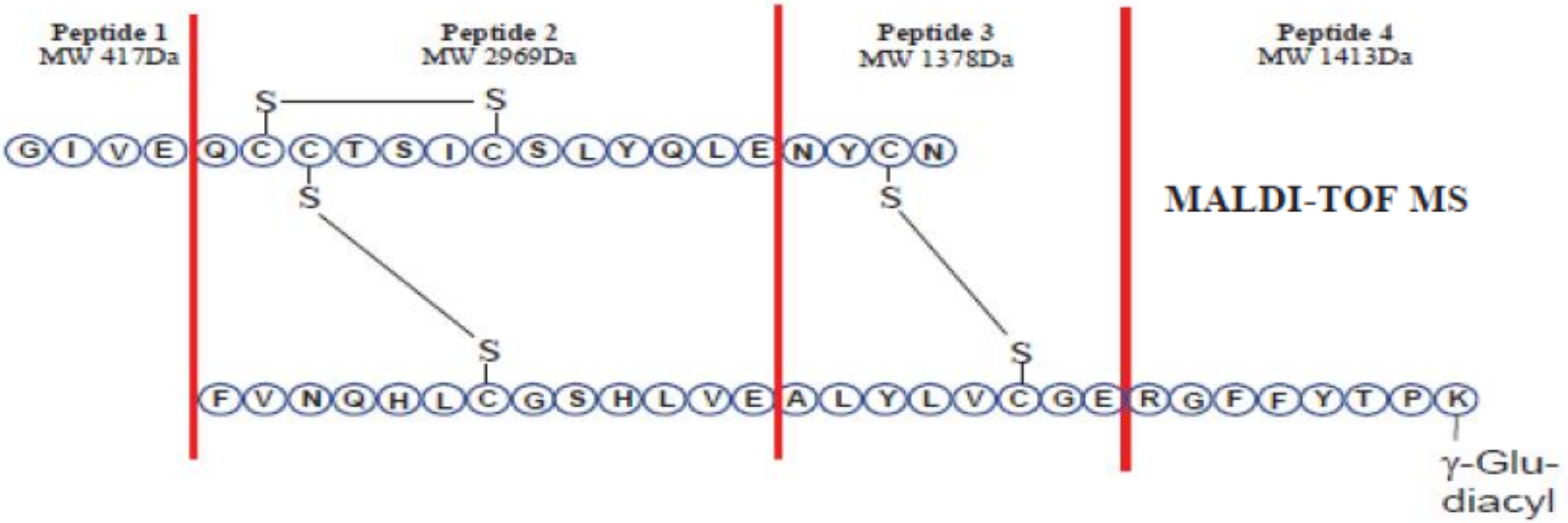
Insulin degludec

Chemical structure; Sequence



Insulin degludec

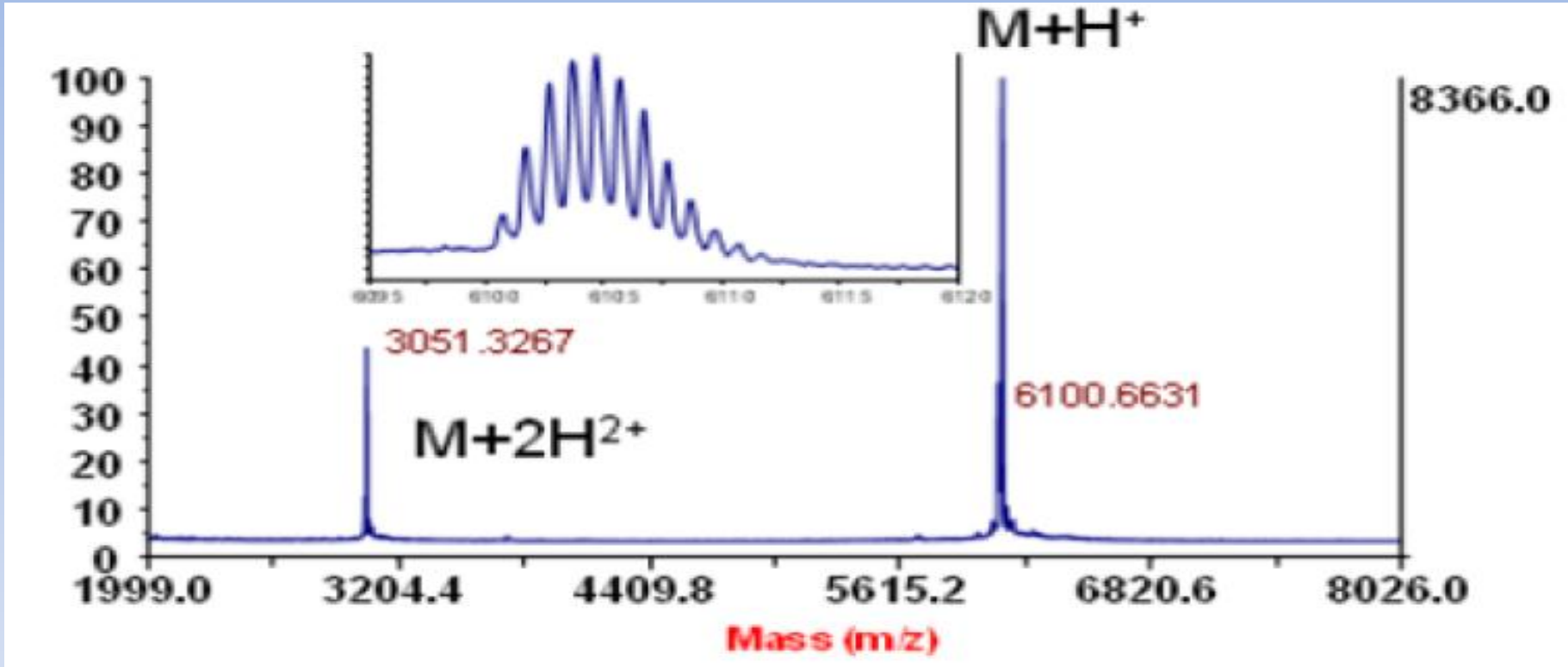
Characterization of Structure by cleavage site after enzymatic cleavage and average mass for the resulting peptides



Description	Peptide 1 +2 (monoisotopic MH+)	Peptide 2 (monoisotopic MH+)	Peptide 3 (monoisotopic MH+)	Peptide 4 (monoisotopic MH+)
Theoretical	3366.52	2968.31	1377.58	1412.78

Determined monoisotopic mass	Theoretical monoisotopic mass
6099.6 Da	6099.8 Da
6099.7 Da	

Insulin degludec
Characterization of Structure by MALDI-TOF-MS



Appearance	Insulin degludec drug substance appears as a white or almost white powder
Isoelectric focusing	The isoelectric point has been experimentally determined by isoelectric focusing to approximately 4.5
pH in aqueous solution	The pH of an aqeous solution of drug substance is approximately 7.4

Case Study Insulin degludec

Case 5:

Insulin Degludec

GIVEQCCTSI CSLYQLENYC
N

FVNQHLCGSH LVEALYLVCG
ERGFFYTPK

Modified

New Peptide
New Protein
New Substance
Amino Acid Sequence
C-Terminus Modification
Structural Modification

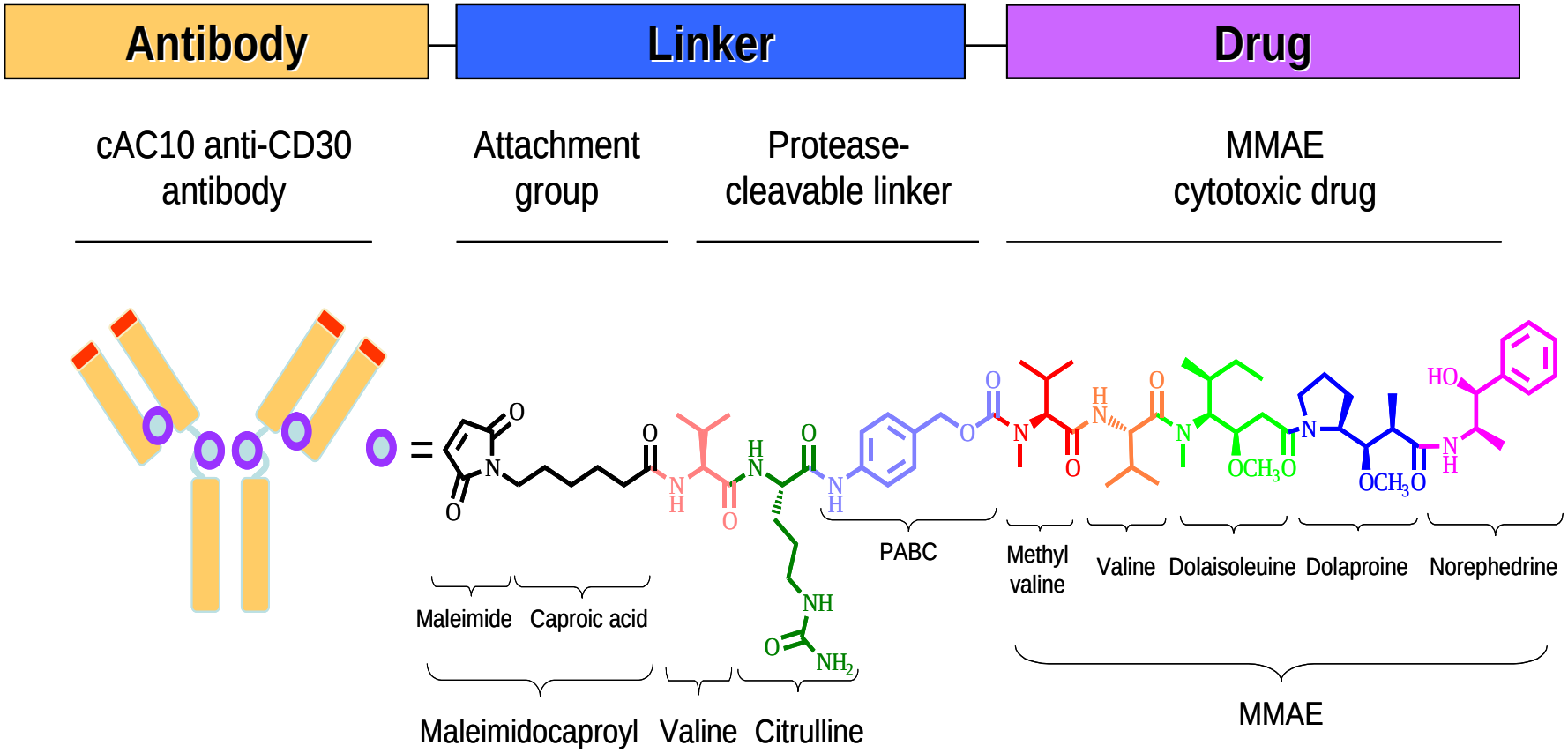
Brentuximab Vedotin

CD30-directed antibody-drug conjugate

- **Description:** Brentuximab vedotin (SGN-35) is an antibody-drug conjugate composed of a C30-directed chimeric form of the monoclonal antibody AC10 (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE) (SGD-1006).
- On average 4 SGD-1006 molecules are conjugated via a covalent thio-ether bond to the cAC10 antibody. Conjugated drug sites are located in the light chain and in the heavy chain, resulting in many active forms with up to 8 possible conjugation sites per antibody.
- So on average: **SGD-35 = cAC10 + 4 SGD-1006. [4av: 2 to 8]**
- Both cAC10 and SGD-1006 are manufactured as stable intermediates. At the end of the process disulfide bridges of cAC10 are reduced on average 2 of the 4 interchain disulfide bonds and SDG-1006 is added in excess, to react with the cAC10-thiols and form the antibody-drug conjugate SGD-35. After quenching of the excess of SDG-1006 with N-acetyl-L-cysteine and diafiltration the bulk is formulated in citrate buffer, trehalose and polysorbate 80.

Schematic structure of SGN-35
cAC10 = Recombinant chimeric heterotetramer form (human IgG1) of the murine monoclonal antibody AC10, which is produced by immunizing mice with the CD30-positive large granular lymphoma cell line

MMAE = monomethyl auristatin E, PABC = p-aminobenzylcarbamate; Cas. Reg. no: 914088-09-8



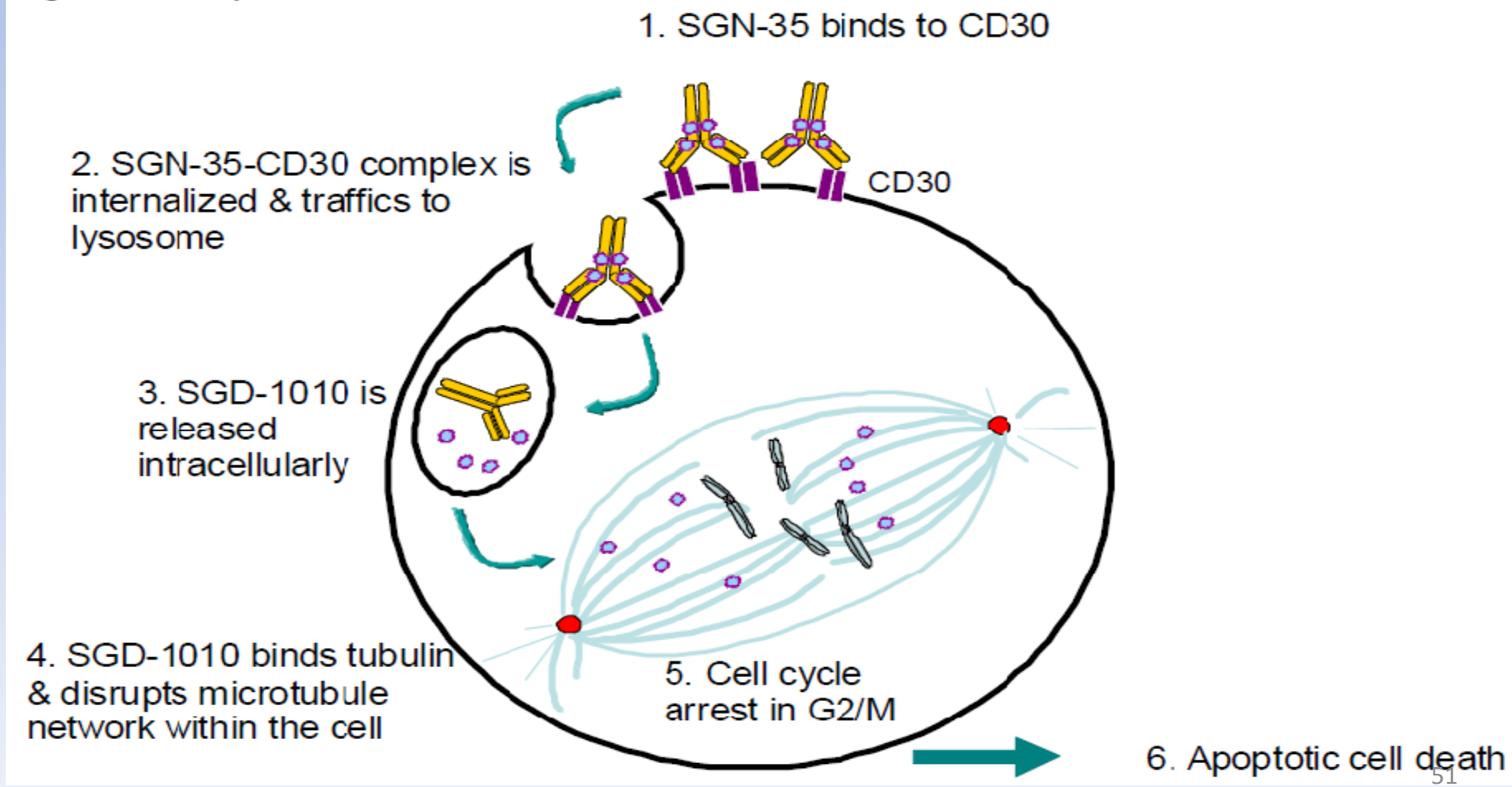
Mol. Formula: C6860 H10532 N1740 O2168 S40; **Mol. Weight:** 153.352 Da

Brentuximab vedotin Pharmacology Brief Summary:

SGN-35 is designed to deliver the cytotoxic agent MMAE specifically to the C30-expressing tumor cells.

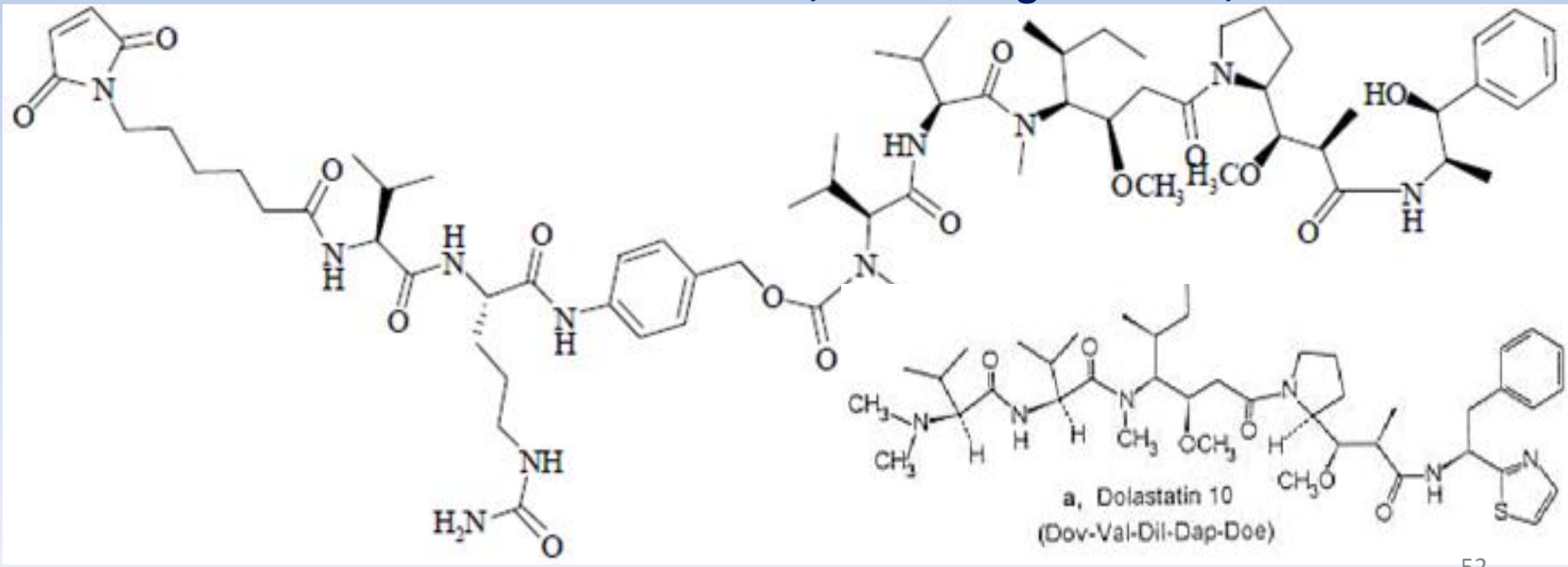
C30, a member of the necrosis factor receptor family, is highly expressed on a subset of lymphomas, including Hodgkin lymphoma.

Figure 1. Proposed mechanism of action of brentuximab vedotin



VEDOTIN Part of the Conjugate

- **Names: Vedotin; Code: SGD-1006;**
  Synonym: N-[6-Maleimidoylcaproyl-L-valyl-L-citrullinyl-4 aminobenzyloxycarbonyl-N-methyl-L-valyl-L-valyl-(3R,4S,5S)-dolaisoleuinyl-(2R,3R,4S)-dolaproinyl]-(1S,2R)-norephedrine;
- Maleimidolcaproyl-valine-citrulline-p-aminobenzyloxycarbonyl-monomethyl auristatin E; [mc-vc-PAB-MMAE]
- **Mol. Formular: C68 H106 N11 O15; Mol. Weight: 1.316,6 Da.**

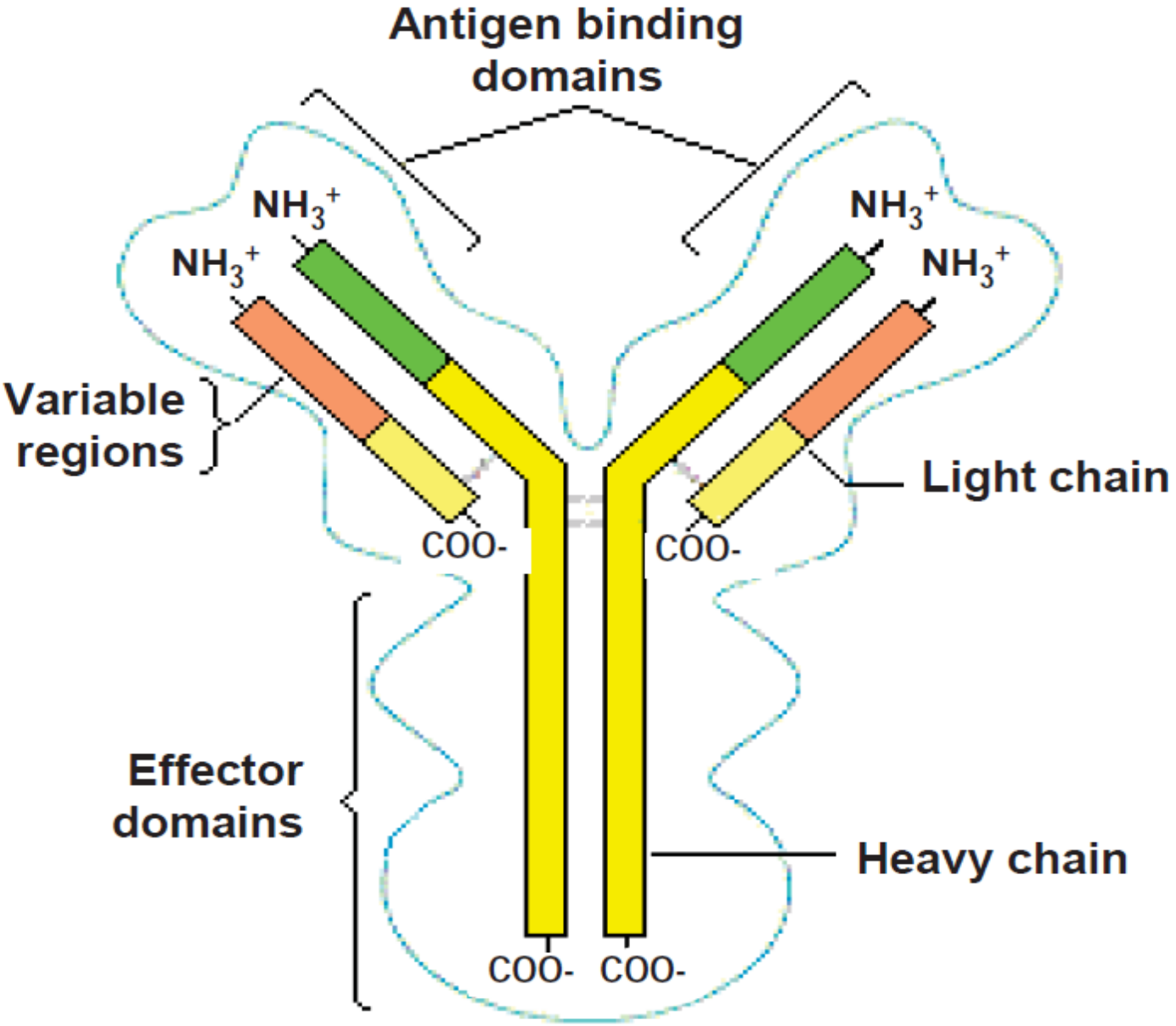


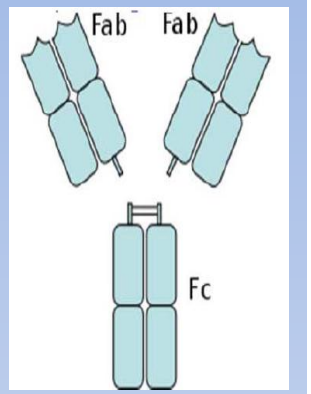
BRENTUXIMAB Part of the Conjugate

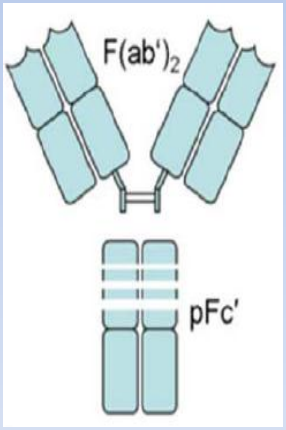
Names and codes:

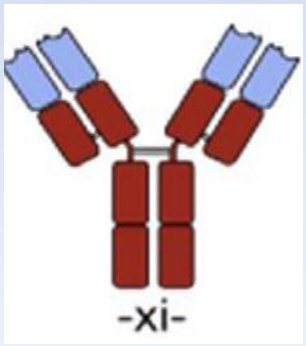
- STNEAsy: Immunoglobulin G1, anti-(human CD30 (antigen)) (human-mouse monoclonal SGN-30 .gamma.1-chain), disulfide with human-mouse monoclonal SGN-30 .kappa.-chain, dimer (CA INDEX NAME); SGN 30
- Chemical Abstracts Service (CAS) Registry Number: **775303-41-8;**
- **Chemical Name(s): Recombinant chimeric immunoglobulin G1 (IgG1)-anti-CD30 monoclonal antibody**
- **Other Non-Proprietary Name(s): SGN-30; Anti-CD30;**
- **Company or Laboratory: Code cAC10;**
- **SmPC: Recombinant chimeric immunoglobulin G1 [IgG1], produced by recombinant DNA technology in Chinese Hamster ovary cells**

Figure 3.2.S.1.2-1 Structure of immunoglobulin G.




Fab
Fab
Fc


F(ab')2
pFc'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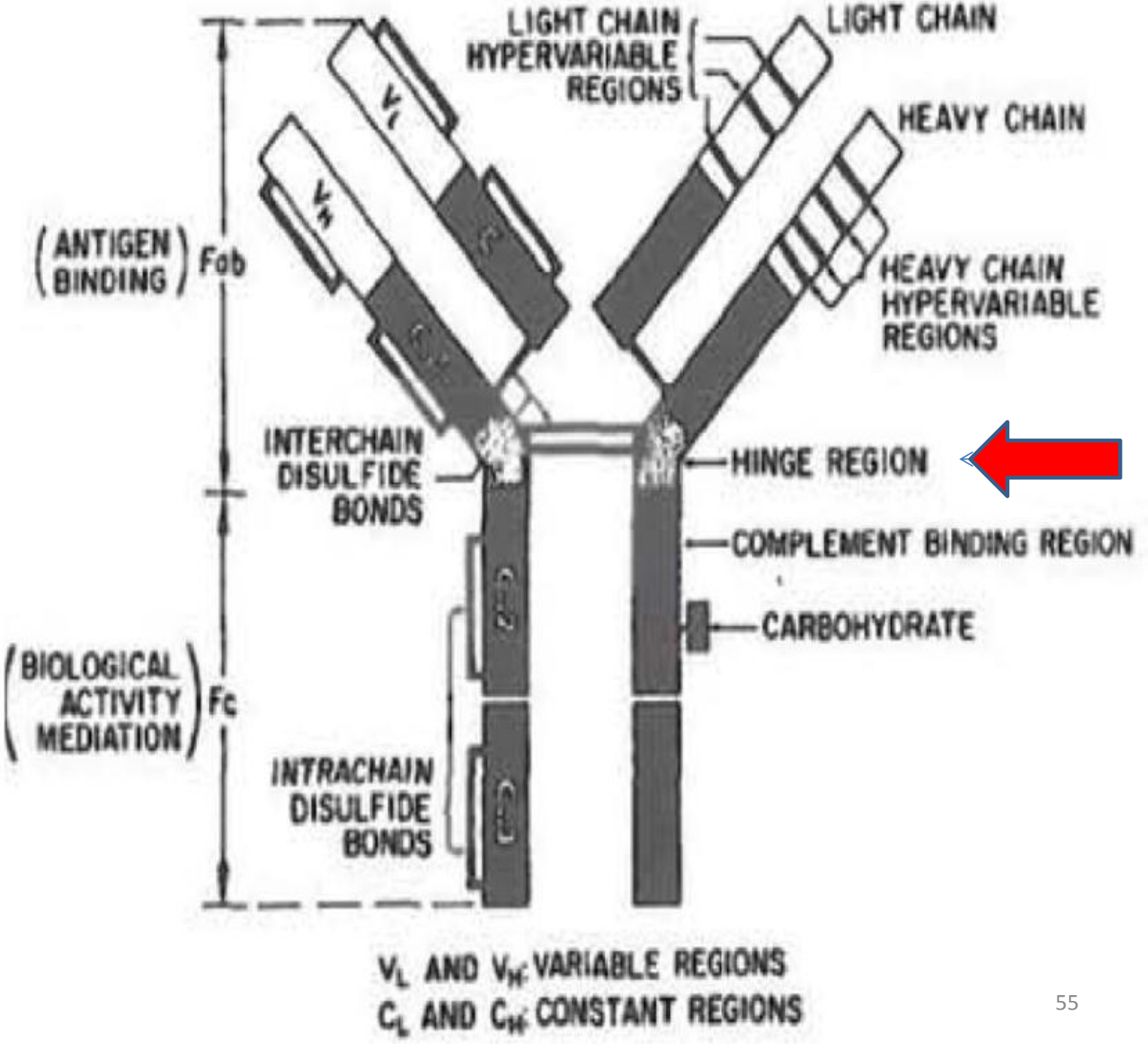

LIGHT CHAIN HYPERVARIABLE REGIONS
LIGHT CHAIN
HEAVY CHAIN
HEAVY CHAIN HYPERVARIABLE REGIONS
(ANTIGEN BINDING) Fab
INTERCHAIN DISULFIDE BONDS
HINGE REGION
COMPLEMENT BINDING REGION
CARBOHYDRATE
(BIOLOGICAL ACTIVITY MEDIATION) Fc
INTRACHAIN DISULFIDE BONDS
VL AND VH: VARIABLE REGIONS
CL AND CH: CONSTANT REGIONS

WHO Drug Information Vol. 24, No. 2, 2010 Proposed INN: List 103

Heavy chain

QIQLQQSGPE VVKPGASVKI SCKASGYTFT DYYITWVKQK PGQGLEWIGW 50
IYPGSGNTKY NEKFKGKATL TVDTSSSTAF MQLSSLTSED TAVYFCANYG 100
NYWFAYWGQG TQVTVSAAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG 446

Light chain

DIVLTQSPAS LAVSLGQRAT ISCKASQSVD FDGDSYMNWY QQKPGQPPKV 50
LIYAASNLES GIPARFSGSG SGTDFTLNIH PVEEEDAATY YCQQSNEDPW 100
TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV 150
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV 200
THQGLSSPVT KSFNRGEC 218

Brentuximab part: Disulfide bridges location:

WHO:
Intra-H 22-96 144-200 261-321 367-425; 22''-96'' 144''-200'' 261''-321'' 367''-425''
Intra-L 23'-92' 138'-198' ;23'''-92''' 138'''-198'''
Inter-H-L * 220-218' 220''-218'''
Inter-H-H * 226-226'' 229-229''
*Two or three of the inter-chain disulfide bridges are not present, the antibody being conjugated to an Average of 3 to 5 drug linkers each via a **thioether bond.**

BRENTUXIMAB Part of the Conjugate

Sequence of the heavy chain and light chain of the Brentuximab part:

Figure 1: Amino acid Sequence of cAC10 Intermediate light chain

```
DIVLTQSPAS LAVSLGQRAT ISCKASQSVD FDGDSYMNWY QQKPGQPPKV LIYAASNLES    60
GIPARFSGSG SGTDFTLNIH PVEEEDAATY YCQQSNEDPW TFGGGTKLEI KRTVAAPSVF   120
IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS   180
STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC                           218
```

Cysteine involved in inter-chain disulfide linkage is indicated by **C**.

Figure 2: Amino acid sequence of cAC10 Intermediate heavy chain

```
QIQLQQSGPE VVKPGASVKI SCKASGYTFT DYYITWVKQK PGQGLEWIGW IYPGSGNTKY    60
NEKFKGKATL TVDTSSSTAF MQLSSLTSED TAVYFCANYG NYWFAYWGQG TQVTVSAAST   120
KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY   180
SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV   240
FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY   300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK   360
NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG   420
NVFSCSVMHE ALHNHYTQKS LSLSPG(K)                                     447
```

Cysteines involved in inter-chain disulfide linkages are indicated by **C**. (K) indicates post-translationally processed C-terminal lysine. **N** indicates glycosylation site.

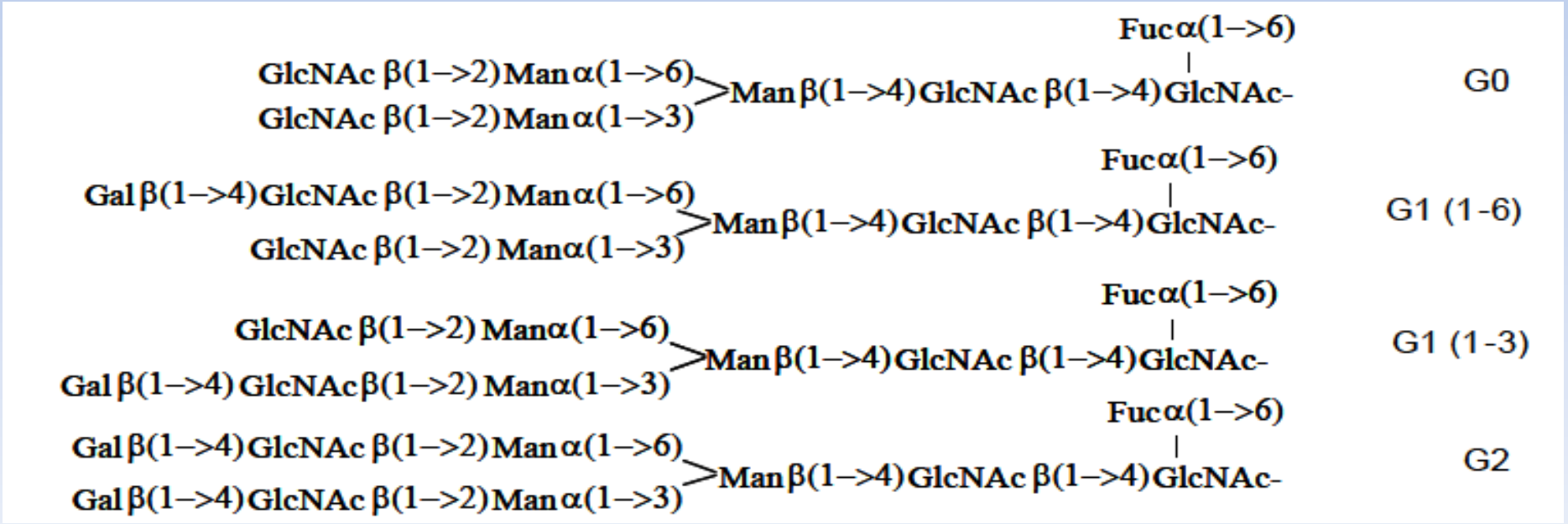
BRENTUXIMAB Part of the Conjugate

- **Disulfide bonds: Twelve intra-chain disulfide bonds** (2 in each light chain and 4 in each heavy chain) and **four inter-chain disulfide bonds** (2 light – heavy and 2 heavy – heavy) are predicted based on the primary sequence of the light and heavy chains.
- **N-glycosylation sites: 297, 297'‘**
  The N-terminal residue of the heavy chain is encoded as a glutamine, but exists mainly in the pyroglutamic acid form. There is one N-glycosylation site on the heavy chain (Asn297), and it is predominantly occupied with a core fucosylated biantennary glycan, typically found with monoclonal antibodies produced by CHO (Chinese Hamster Ovary) cells, with 0, 1 or 2 terminal galactose residues.
  Glycosylation Occupancy: Asn297 is occupied for 97%.
  Monosaccharide Composition: Neutral monosaccharides (fucose, galactose, glucose and mannose); Basic monosaccharides (galactosamine, glucosamine) and sialic acid was released from the antibody using acid hydrolysis.
  N-Glycan Distribution: The predominant N-linked glycoforms detected are core fucosylated biantennary glycans with 0, 1, and 2 terminal galactose residues (G0, G1, and G2). Together, these forms comprise 88% of the N-linked glycans detected.

Brentuximab
Schematic depiction of identified N-linked glycans

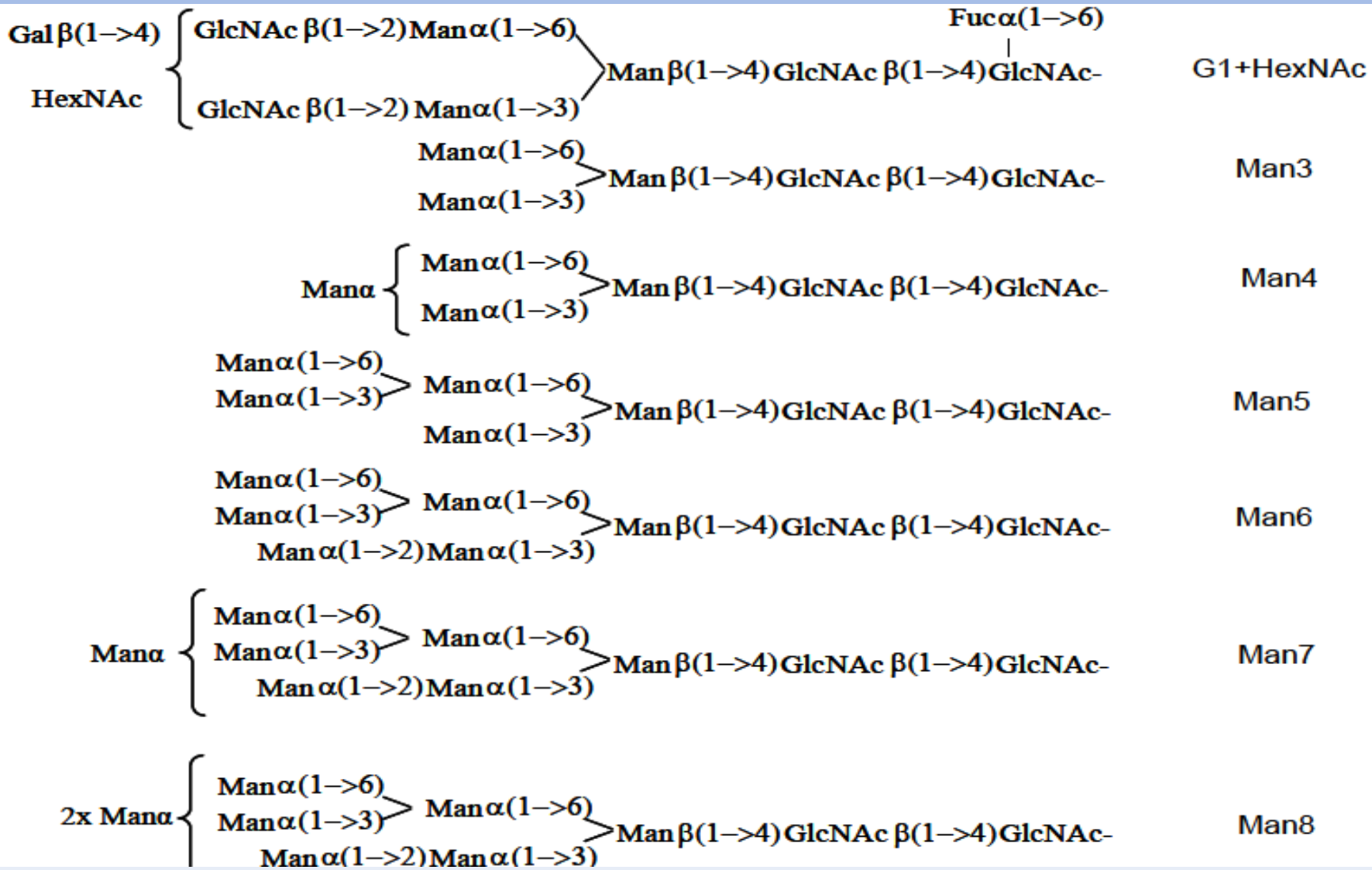
- A: Core fucosylated biantennary glycans (G0,G1,G2) [89%]
- B: A-(non) fucosylated G0 (G0-F) and oligomannose structures (Man3, Man5, Man6, and Man8); G0 lacking a terminal N-acetylglucosamine (G0-1).
- The balance Fucosylated/ aFucosylated Glycans affects the Complement Dependent Cytotoxicity (CDC) of the Mab.

  [Complement-Dependent Cytotoxicity (CDC) Cell-Based Assay]



Brentuximab

Schematic depiction of identified N-linked glycans



LYS-C PROTEOLYSIS AND REDUCTION

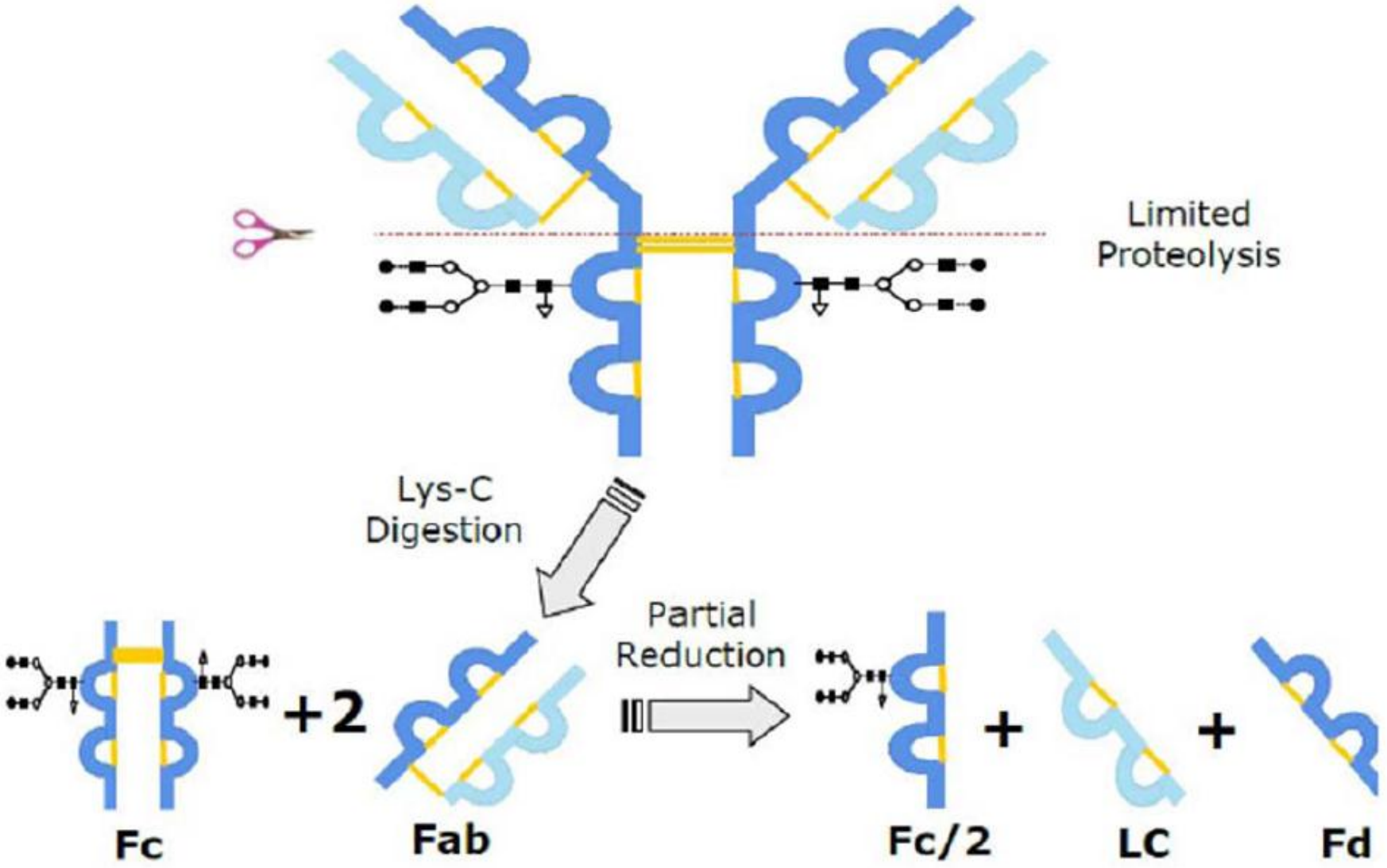
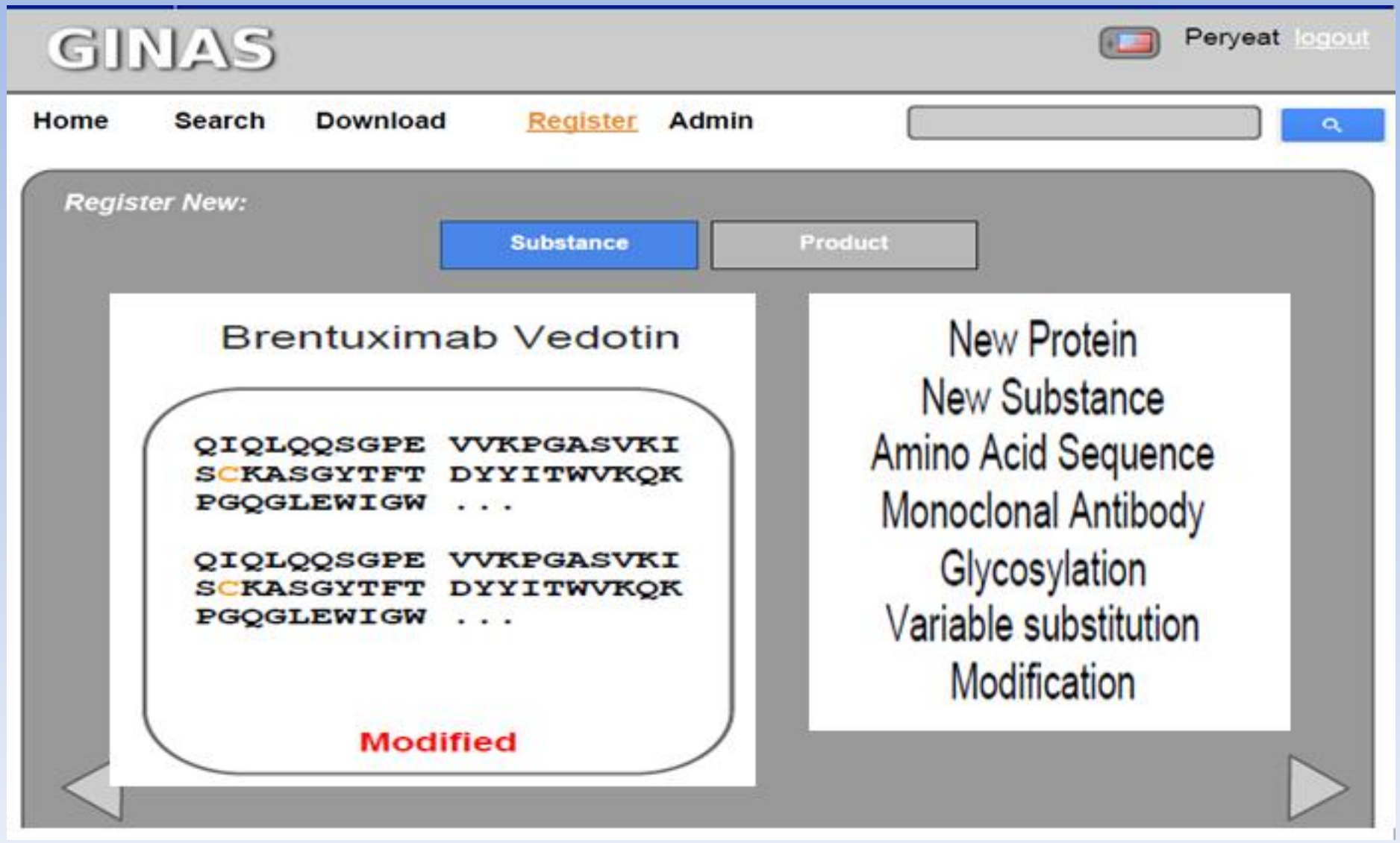


Figure 1. Fragments generated by limited proteolysis o
monoclonal antibody with Lys-C followed by partial reduction.

Case Study Brentuximab Vedotin



CBG MEB

THANK YOU FOR YOUR ATTENTION

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<h.diederik@cbg-meb.nl>

Miss Ing. C.G. Matai, Chemist
<cg.matai@cbg-meb.nl>

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3503 RG Utrecht,
The Netherlands

Case studies: RITONAVIR

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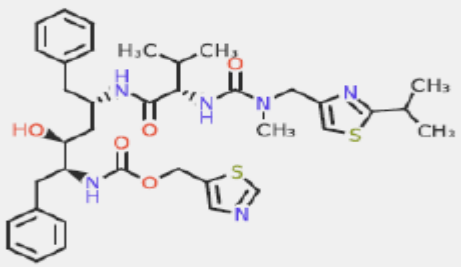
Substance Product

Ritonavir



New Group 1 Specified Substance
New Substance
Physical Forms
References
Physical Properties

Case studies: Brentuxumab Vedotin

GINAS

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Substance | Product

Brentuximab Vedotin

QIQLQQSGPE VVKPGASVKI
SCKASGYTFT DYYITWVKQK
PGQGLEWIGW ...

QIQLQQSGPE VVKPGASVKI
SCKASGYTFT DYYITWVKQK
PGQGLEWIGW ...

Modified

New Protein
New Substance
Amino Acid Sequence
Monoclonal Antibody
Glycosylation
Variable substitution
Modification